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Hormonal consequences, replacement therapy, and lost workdays after cervical cancer treatment

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HORMONAL CONSEQUENCES, REPLACEMENT THERAPY, AND LOST WORKDAYS AFTER CERVICAL CANCER TREATMENT

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ABSTRACT

Background: Uterine cervical cancer affects women of all ages and has a generally favorable prognosis. Many survivors live long with the consequences of the disease and its treatment, and therefore it is important to characterize potential treatment-induced morbidity.

Aims: To investigate different hormonal aspects and work loss among cervical cancer survivors, by treatment modality.

Methods: In a pilot study, we analyzed serum levels of anti-Müllerian hormone (AMH) and follicle-stimulating hormone (FSH) as measurements of ovarian function, as well as estradiol and androgens in serum, and assessed sexual function before and after treatments in a one-year cohort of cervical cancer patients (N = 71). We also used Swedish national registers to investigate use of hormone therapy after cervical cancer treatment, and lost workdays due to sick leave and disability pension among 837 and 1971 patients, respectively.

Results: Serum levels of AMH were undetectable one year after salpingo-oophorectomy or radiotherapy among patients < 45 years of age at diagnosis. After radical hysterectomy and pelvic lymphadenectomy with ovarian preservation, AMH declined, whereas no change was found in serum levels of FSH. Circulating levels of total and free testosterone decreased after pelvic radiotherapy among pre- as well as postmenopausal women. No correlations were found between androgen levels and female sexual function index (FSFI) scores following treatment. Among women with estrogen deprivation due to salpingo-oophorectomy or radiotherapy, 67% had at least one dispensing of hormone therapy during the period 0.5 to 1 year after diagnosis, and 46% dispensed at least 75% of the recommended dose. The proportion of users decreased during follow-up. Relapse-free cervical cancer patients had more lost workdays than matched comparators from the general population for 4 years following diagnosis, and were at increased risk of disability pension following hysterectomy or chemo/radiotherapy. Women treated with fertility-sparing surgery did not have more lost workdays than the comparators beyond the first year and were not at increased risk of disability pension.

Conclusions: Serum levels of AMH were reduced after radical hysterectomy with ovarian preservation, indicating a possible risk of early ovarian failure. Testosterone in serum was reduced after radiotherapy, but was not associated with sexual function in this pilot setting. Less than half of cervical cancer survivors likely to have therapy-induced early menopause used hormone therapy at, or close to, the recommended dose, and the use decreased during follow-up. All treatment modalities for cervical cancer except fertility-sparing surgery were associated with long-term work disability.

MeSH terms: *uterine cervical cancer; anti-Müllerian hormone; hysterectomy; androgens; testosterone; sexual dysfunction; hormone replacement therapy; premature menopause; radiotherapy; oophorectomy; sick leave*

LIST OF SCIENTIFIC PAPERS

- I. Hallqvist Everhov A, Bergmark K, Smedby KE, Hirschberg AL, Flöter Rådestad A.
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- III. Everhov AH, Nyberg T, Bergmark K, Citarella A, Rådestad AF, Hirschberg AL, Smedby KE.
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- IV. Everhov AH, Ekberg S, Hirschberg AL, Bergmark K, Flöter Rådestad A, Glimelius I, Smedby KE.
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LIST OF ABBREVIATIONS

A	Androstenedione
AIDS	Acquired immunodeficiency syndrome
AMH	Anti-müllerian hormone
BMI	Body mass index
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CT	Computed tomography
DDD	Designated daily dose
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulphate
DHT	Dihydrotestosterone
EORTC	The European organization for research and treatment of cancer
FAI	Free androgen index
FAIS	Female androgen insufficiency syndrome
FIGO	International federation of gynecology and obstetrics
FSFI	Female sexual function index
FSH	Follicle-stimulating hormone
FT	Free testosterone
GnRH	Gonadotropin releasing hormone
Gy	Gray
HPO	Hypothalamic-pituitary-ovarian
HPV	Human papilloma virus
HR	Hazard ratio
HSDD	Hypoactive sexual desire disorder
HT	Hormone therapy
ICD	International classification of diseases
IR	Incidence rate
IVF	In vitro fertilization
LAVH	Laparoscopy-assisted radical hysterectomy
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LH	Luteinizing hormone
LISA	Longitudinal integration database for health insurance and labour market studies
MIDAS	Mikrodata för analys av socialförsäkringen
MRI	Magnetic resonance imaging
NBHW	National board of health and welfare
NOCECA	Nordic society for gynecological oncology protocol for the treatment of cervical cancer stage IIb-IVa
NPR	National patient register
OR	Odds ratio

Abbreviations

PET	Positron emission tomography
POI	Premature ovarian insufficiency
RAVH	Robot-assisted radical hysterectomy
RR	Relative risk
SFQ	Sexual function questionnaire
SHBG	Sex steroid-hormone binding globulin
SIR	Standardized incidence ratio
SOE	Salpingo-oophorectomy
SSIA	The Swedish social insurance agency
TGF	Transforming growth factor
TPR	Total population register
TT	Total testosterone

INTRODUCTION

Cancer survivorship issues are becoming increasingly important, due to a general increase in cancer incidence [1] and an improved cancer survival [2]. Uterine cervical cancer has a favorable prognosis, especially at younger ages [3], and therefore many patients will have a long life expectancy after treatment. The overall aim of this thesis was to examine side effects of treatments among cured patients. About half of all women diagnosed with cervical cancer are under 50 years of age, and for these women, treatment often leads to permanent loss of fertility and early menopause. Therefore, hormonal aspects are of special concern in this patient group. The majority of the women diagnosed with cervical cancer are also in their working ages, and the ability to work following cancer diagnosis and treatment is an important part of the restoration to health.

The background chapter gives an introduction to cervical cancer and its treatment and the regulation and importance of sex hormones in women. It also presents a summary of what is known, and not known, about treatment effects on hormone levels, and the possible consequences of reduced hormone levels. Recommendations for the use of hormone therapy in general, and after cervical cancer are described. The chapter also includes a short overview of morbidity and patient-reported distressful symptoms after treatment, which may have implications for quality of life as well as long-term work ability in cervical cancer patients. Finally, studies evaluating work loss among cancer patients in general, and among gynecologic or cervical cancer survivors in particular, are summarized.

The four studies in the thesis aim to investigate hormonal changes during the first year following diagnosis and treatment (studies I and II), use of hormone therapy among women in therapy-induced early menopause (study III) and work loss (study IV) among survivors.

BACKGROUND

UTERINE CERVICAL CANCER

Incidence

In 2012, uterine cervical cancer was the 4th most common cancer among women worldwide, with an absolute majority of cases and deaths in low-income countries (Figure 1) [4]. In high-income countries, incidence and mortality from cervical cancer have decreased over the past decades following the introduction of screening programs [5]. In Sweden, cytologic screening was introduced successively starting in 1964, and has led to increased survival rates, probably due to an earlier detection [6, 7]. The annual incidence has declined from 25 cases/100,000 person years in 1965 to 8.4/100,000 person years in 2012 [8]. In 2013, 468 women were diagnosed with cervical cancer, of which 56% were under 50 years and 36% under 40 years [9].

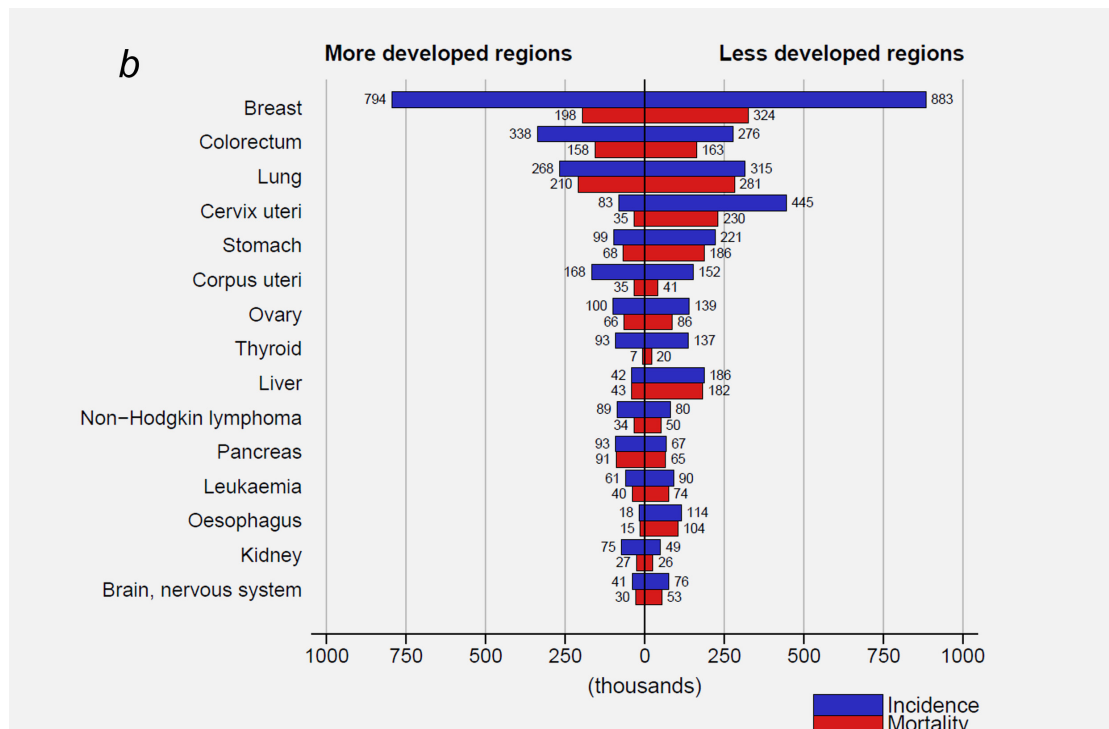


Figure 1. Estimated cancer incidence and mortality in women in more developed regions (Europe, North America, Australia/New Zealand, Japan) and less developed regions (Africa, Asia excluding Japan, Latin America, The Caribbean, Melanesia, Micronesia, Polynesia) of the world in 2012. From Ferlay et al. 2014 [4] with permission.

Symptoms and spread

The cervix is anatomically defined as the lower third of the uterus. Cancer originates from the vaginal surface or the canal [10], but usually starts in the metaplastic epithelium of the cervical transformation zone, where the squamous epithelium of the ectocervix replaces the columnar epithelium of the endocervix (squamo-columnar junction) [11]. Early cancers can go without symptoms, but coital or stress bleeding and discharge is common. Weight loss and pain are signs of advanced tumor stages [12]. Untreated cervical tumors grow in continuity into the paracervical tissues and pelvic organs, spread to regional lymph nodes (parametrial, obturator, internal iliac, external iliac, presacral, common iliac) and metastasize to distant organs (aortic and mediastinal lymph nodes, lungs, and skeleton)[10].

Histopathology

Almost all cervical tumors are of epithelial origin and can roughly be divided into squamous cell cancer (80%) and adenocarcinoma (20%) [13]. Squamous cell cancer can be further classified into keratinizing, non-keratinizing, basaloid, verrucous, warty, papillary, lymphoepithelioma-like, and squamotransitional subtypes. Adenocarcinomas are sub-divided into mucinous, endometrioid, clear cell, serous and mesonephric subtypes [14]. Over the past 50 years there has been an increase in the relative proportion of adenocarcinoma in Sweden [15]. One suggested explanation is that the current screening methods are less effective in discovering adenocarcinoma as compared to squamous cell cancer [15]. More unusual tumors are, for instance, glassy cell carcinoma and neuroendocrine (small cell) carcinoma, which have a worse prognosis than other histological subtypes [16, 17].

Etiology

Human papilloma virus (HPV) is considered the causal factor for cervical cancer [18]. HPV is found in practically all cases of squamous cell carcinoma and adenocarcinoma [18, 19], with the exception of rare subtypes such as gastric, mesonephric adenocarcinoma and clear cell carcinoma [20-22]. The association between HPV and cervical cancer was first noted by the German virologist Harold zur Hausen in the 1970s [23], and he was rewarded the Nobel Prize in 2008 for this discovery.

HPV types are divided into low- and high cancer risk types, since they exhibit different disease-causing characteristics. Fifteen HPV types are classified as high risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 [24]. HPV infection is considered “necessary but not sufficient” [11] for the progression through the precancerous stages low and high grade intraepithelial lesion, (previously called cervical intraepithelial neoplasia, CIN, 1, 2 and 3) to invasive cancer, but the exact co-factors necessary for the malignant transformation are not known. There is also considerable spontaneous healing of both HPV infection and precancerous lesions [25].

Long before the discovery of HPV, it was noted that cervical cancer was mainly diagnosed in younger women with many children, whereas endometrial cancer was diagnosed later in life in childless women [26]. Reproductive and other factors have, since then, been further evaluated in detail. In a meta-analysis from 2007 with data from 12 epidemiological studies, the risk of cervical cancer increased with the number of full-term pregnancies, the number of sexual partners, low age at first intercourse, low age at first birth, use of oral contraceptives, and smoking (Table 1) [27].

Table 1. Risk factors for squamous cell carcinoma and adenocarcinoma versus cervical cancer free controls. Relative risks (RR) were stratified by study, age at diagnosis, number of sexual partners, age at first intercourse, number of full-term pregnancies, smoking status, previous Pap smear (yes/no), and duration of oral contraceptive use. Bold numbers are significantly different between cancer patients and controls. Extracted from Table 2, International Collaboration of Epidemiological Studies of Cervical Cancer, 2007 [27], with permission.

	Squamous cell carcinoma vs cancer-free controls RR (95% CI)	Adenocarcinoma vs cancer-free controls RR (95% CI)
Number of full-term pregnancies		
Nulliparous	0.69 (0.60–0.78)	0.94 (0.74–1.18)
1-2	1.00 (0.94–1.07)	1.00 (0.89–1.13)
3-4	1.50 (1.43–1.59)	1.36 (1.22–1.52)
5+	2.08 (1.95–2.23)	1.61 (1.37–1.90)
Number of sexual partners		
1	1.00 (0.94–1.06)	1.00 (0.88–1.14)
2-5	2.00 (1.91–2.09)	1.63 (1.47–1.80)
6+	2.98 (2.62–3.40)	2.64 (2.07–3.36)
Age at first intercourse		
21+	1.00 (0.93–1.07)	1.00 (0.86–1.16)
18-20	1.60 (1.51–1.68)	1.50 (1.35–1.67)
<18	2.24 (2.11–2.38)	2.06 (1.83–2.33)
Age at first birth		
Nulliparous	0.85 (0.75–0.97)	1.14 (0.91–1.44)
25+	1.00 (0.93–1.08)	1.00 (0.86–1.16)
20-24	1.66 (1.57–1.74)	1.44 (1.30–1.60)
17-19	2.16 (2.03–2.30)	2.10 (1.84–2.40)
<17	2.72 (2.42–3.05)	2.01 (1.53–2.65)
Duration of oral contraceptive use		
Current users	1.08 (1.06–1.09)	1.07 (1.04–1.11)
2-9 years since stopping	1.03 (1.02–1.05)	1.03 (1.00–1.06)
10+ years since stopping	0.98 (0.96–1.00)	1.02 (0.97–1.07)
Smoking		
Never	1.00 (0.94–1.06)	1.00 (0.89–1.13)
Past	1.01 (0.91–1.14)	0.74 (0.60–0.92)
Current	1.50 (1.38–1.63)	0.86 (0.73–1.01)

Female sex hormones have been suggested as risk factors for cervical cancer, due to the observed associations with reproduction, use of contraceptives and cervical cancer [27]. Studies have also suggested an association between an increased risk of cervical adenocarcinoma and postmenopausal hormone therapy (HT) [28, 29]. Association between sex hormones and cervical cancer has been supported by cell-line experiments, where both estrogen and progesterone promoted cervical cancer cell proliferation, which in turn made the cells vulnerable to mutations [30]. Apart from direct cellular effects, a potential biological explanation for the association between sex hormones and cervical cancer, is that high levels of estrogen or progesterone/progestogen, either due to oral contraceptives or pregnancy, can cause ectopy at the squamo-columnal junction, making it more accessible to HPV-infection [31].

Current smoking is associated with squamous cell carcinoma, but not adenocarcinoma [32]. Proposed mechanisms include local genotoxic effects on the cervical epithelium that stimulate carcinogenesis, or localized immunosuppression. Immunological factors are known to affect cancer progression in general, and patients with severe immunosuppression, either due to acquired immunodeficiency syndrome (AIDS) or to medication, as in the case of organ transplant recipients, have an increased risk of cervical cancer [33].

However, the associations between cervical cancer and several of the risk factors mentioned above may be confounded. The use of contraceptives, smoking, multi-parity, early sexual debut, and numerous sexual partners may all be associated with a behavior that increases the risk of encountering a partner with HPV. Therefore, evaluation of independent risk factors for cervical cancer should ideally be restricted to HPV-positive women. Established risk factors for cervical cancer among HPV-positive women are: oral contraceptive use more than 5 years [34], current cigarette smoking [32], multi-parity (increasing risk with increasing number of children), age at first full-term pregnancy (increasing risk with decreasing age) [35] and co-infection with chlamydia trachomatis and herpes simplex [36].

Primary and secondary prevention

Three HPV vaccines for the prevention of cervical cancer are approved for clinical use – Cervarix®, Gardasil®, and Gardasil 9®. All vaccines are aimed at HPV 16 and 18 for their predominant role in cancer development, and have shown protection against precancerous lesions [37-39]. Gardasil® also protects against HPV 6 and 11 infection, and Gardasil 9® against HPV 6, 11, 31, 33, 45, 52, and 58 [39]. The Swedish National Board of Health and Welfare (NBHW) decided in 2008 that HPV vaccination should be included in the national vaccination program, and it is now offered to girls aged 10-12 years.

The destruction of precancerous lesions is a secondary prevention of cervical cancer that has been used since the construction of the colposcope (a lighted binocular microscope used to magnify the view of the cervix) by Hinselman in 1924 [26]. During the same decade, the cytologist Papanicolaou discovered that after brushing the cervix and studying the smear under microscope, cancer precursor cells could be detected. His discoveries led to the gynecological mass screening programs that started in the 1960's [40]. Vaginal cytology is still used today and referred to as Papanicolaou or Pap smear. Swedish women are offered Pap smear between 23 and 60 (or 65) years of age. From 2010 liquid-based cytology has been used, which also allows HPV-testing [41]. Cervical tumors in women above screening age are discovered at more advanced stages, why an extension of current cervical screening program beyond 65 years has been proposed [42].

Diagnosis and staging

Staging of cervical cancer is based on clinical evaluation of the size of the tumor and its extension into and beyond the pelvis at the time of primary diagnosis. According to the International Federation of Gynecology and Obstetrics (FIGO) staging system (Table 2) [3, 43], clinical examination – preferably under anesthesia – including biopsy and the use of endoscopy and plain x-rays are permitted methods of staging. Other, more advanced examinations, such as Magnetic resonance imaging (MRI) or Positron emission tomography (PET) scans are encouraged but not mandatory, since they are not available in all countries. Findings from MRI or PET do not change the clinical stage [3, 43]. The American Joint Committee on Cancer TNM cancer staging system [44] is similar to the FIGO system. It classifies cervical cancer based on three factors: the extent of the tumor (T), cancer spread to lymph nodes (N), and cancer spread to distant sites (M), by findings from surgery or imaging (Table 2).

In Sweden, women with cervical cancer are diagnosed by way of biopsy. The tumor staging is based on clinical examination under anesthesia, and typically the women do an MRI of the pelvis, and computed tomography (CT) of the thorax and abdomen. For tumors larger than 4 cm, or suspected growth beyond the cervix, PET-CT is usually also performed.

Table 2. The FIGO nomenclature [3, 43] and the TNM cancer staging system [44]. The FIGO staging system is the one used by gynecologists internationally.

Primary tumor (T)		
TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to the cervix (disregard extension to the corpus)
T1a	IA	Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less
T1a1	IA1	Measured stromal invasion ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread
T1a2	IA2	Measured stromal invasion > 3.0 mm and ≤ 5.0 mm with a horizontal spread ≤ 7.0 mm
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T1b2	IB2	Clinically visible lesion > 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T2a2	IIA2	Clinically visible lesion > 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctional kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctional kidney
T4	IV	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis
T4a	IVA	Tumor invades mucosa of bladder or rectum
T4b	IVB	Tumor extends beyond true pelvis
Regional lymph nodes (N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
Distant metastasis (M)		
M0		No distant metastasis
M1		Distant metastasis (including peritoneal spread; involvement of supraclavicular, mediastinal, or paraaortic lymph nodes; and lung, liver, or bone)

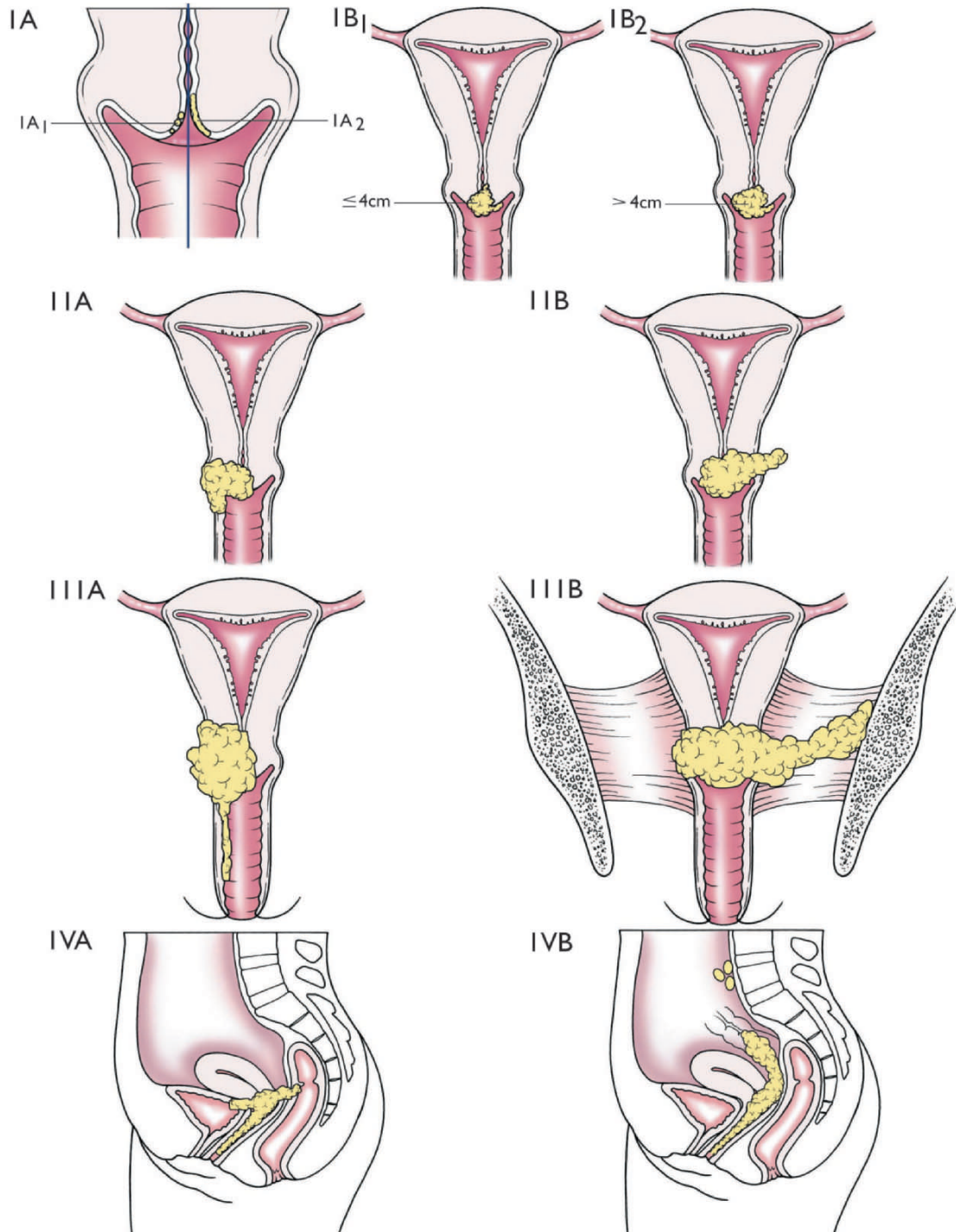


Figure 2. Cervical cancer stages IA to IVB according to FIGO. From Quinn et al. [3], with permission.

Treatment recommendations

Swedish cervical cancer treatment guidelines are developed by health professionals in collaboration with the six regional cancer centers. Treatment procedures differ only slightly between regions [41, 45-49]. National guidelines are under development. Cancer treatment can be surgical, oncological, or a combination, depending on stage and histopathology findings.

Early stages

For stage IA1 (micro-invasive cancer, only visible through microscopic evaluation of biopsy material) simple hysterectomy is recommended, and can be performed either abdominally or vaginally. Conization is an alternative if fertility is desired.

For stage IA2 to IB1 and IIA (from micro-invasive tumors with stromal invasion > 3 mm up to clinically visible tumors, but without parametrial invasion) radical hysterectomy and pelvic lymphadenectomy (due to the risk of lymph node metastases) is recommended. If fertility is desired, and tumor size is less than 2 cm, radical trachelectomy plus laparoscopic lymphadenectomy can be performed. Radical vaginal trachelectomy, first described by the French gynecologist Dargent in 1986, consists of removal of the cervix, parametrial tissue and upper part of the vagina. The cervix is transected 1 cm above the tumor margin and only the vaginal branch of the uterine artery is ligated. A prophylactic cerclage is sometimes inserted with a non-resorbable stitch [50].

The radical hysterectomy usually performed in Sweden - Piver type II [51] or Querleu/Morrow type B [52] - is based on the operative techniques first performed by Reis and Clark at Johns Hopkins Hospital in the mid 1890's [53] and later developed by Wertheim (1912) and Meigs (1951) [54]. The purpose of the modified radical hysterectomy, as described in the article by Piver from 1974 [51], is to remove paracervical tissue, but preserve blood supply to the distal ureters and bladder. The uterosacral ligaments are resected midway between the uterus and the sacral attachments, and the medial half of the cardinal ligament and the upper 1/3 of the vagina are removed. Pelvic lymphadenectomy is performed at the external iliac, internal iliac, common iliac and obturator fossa [52, 54]. Ovarian preservation is considered safe in early stages [55]. Studies on minimally-invasive surgery by means of laparoscopy-assisted radical hysterectomy (LAVH) [56] or robot-assisted laparoscopic hysterectomy (RAVH) [57, 58] indicate shorter length of hospital stay and time to normal daily activity for the patients compared with open surgery, however, due to the lack of randomized clinical trials, these methods are not yet recommended in general clinical practice [59]. The sentinel node technique may in the future reduce the use of total regional lymphadenectomy [60].

When surgery is chosen as primary treatment, adjuvant radiotherapy plus chemotherapy is typically given in case of positive lymph nodes, growth in parametria or positive surgical margins, large tumor volume, capillary involvement or growth in the outer 1/3 of the cervical stroma [45, 61].

Advanced stages and recurrent disease

For stages IB2, IIB, III, and IVA (locally advanced tumors with increasing degrees of parametrial invasion up to invasion of the vagina/ureters/bladder and rectum) standard primary treatment is external beam radiotherapy plus intracavitary radiotherapy (brachytherapy) with concurrent weekly cisplatin chemotherapy [62, 63]. A Nordic protocol for CT-based external beam radiotherapy in locally advanced cervical cancer – NOCECA – was initiated in 1994 [64, 65]. The pelvic field for the external beam radiotherapy in NOCECA includes the internal and external iliac nodes and the lower common iliac nodes up to the level of the space between lumbar vertebrae L4 and L5. The treatment is delivered with a daily fraction of 1.8-2.0 Gray (Gy) over a period of 5 to 6 weeks. The total external radiotherapy dose is 45-50 Gy to the adjuvant targets (lymph nodes) and 50-56 Gy to the tumor target, depending on the number of brachytherapy insertions (usually two to three are given). During later years the use of MRI for three-dimensional treatment planning has allowed more exact individual adaptation of dose to target organs (clinical target volume [66]), and has been shown to improve local control and reduce morbidity [67, 68]. Extended field radiation should be considered in patients with positive common iliac or aortic lymph nodes.

Ovarian transposition before start of pelvic radiotherapy is an attempt to preserve ovarian function in younger women. The infundibulopelvic ligament including ovarian vessels is mobilized and each ovary is placed as high as possible with the least possible tension, preferably in the paracolic gutters 1.5 cm above the iliac crest. Surgical clips are applied to the upper and lower borders of each transposed ovary, so their position can be identified on X-ray [69].

Total pelvic exenteration can be performed in patients with recurrence after irradiation or with primary stage IV disease, if the tumor has advanced into the bladder and rectum but remains confined to the pelvis. The procedure involves en bloc resection of all pelvic structures. If the tumor grows only anteriorly, the rectum can be left intact by removing the bladder and uterus— anterior exenteration. Posterior exenteration means to remove the uterus and rectum but leaving the urinary bladder intact [70].

For stage IVB (distant metastases) or recurrent disease the prognosis is poor [3]. Distant metastases can be treated with palliative chemotherapy, often cisplatin in combination with topotecan [71] or paclitaxel [72]. The response rate of chemotherapy is lower in patients with disease recurrence in a previously irradiated pelvis [73], due to disruption of the pelvic blood supply.

Prognostic factors

The FIGO 26th annual report [3] identified several prognostic factors associated with overall survival in 11775 women from 37 countries treated 1999-2001 (mean age 52 years). Stage was the most important independent prognostic factor. Patients with early tumors (stage IA1) had a 5-year survival of 98% compared to 9% for patients in stage IVB. The presence of lymph node metastases reduced 5-year survival to 64% compared to 92% for patients without lymph node metastases. In the multivariate analysis (Table 3), age (≥ 50 versus < 50 years) was associated with a worse outcome only in stage I disease. Squamous cell cancer was associated with a better outcome than adenocarcinoma. Tumor size and lymph node status were predictors of worse outcome primarily among patients diagnosed in stages I-II.

Table 3. Multivariate analysis of patients treated in 1999-2001, adjusted for country and stratified by age, histological type, grade, tumor size, lymphovascular space involvement, and lymph node status. Extracted from table 12, Quinn et al., 2006 [3], with permission.

	Hazard ratio (95%CI)			
	Stage I	Stage II	Stage III	Stage IV
Age				
<50	1 (ref)	1 (ref)	1 (ref)	1 (ref)
≥ 50	1.4 (1.2–1.7)	1.0 (0.9–1.1)	1.0 (0.9–1.2)	1.0 (0.9–1.3)
Histology				
Squamous cell	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Adenocarcinoma	1.9 (1.6–2.4)	1.4 (1.1–1.7)	1.5 (1.2–1.9)	1.5 (1.1–2.0)
Tumor size				
≤ 4	1 (ref)	1 (ref)	1 (ref)	1 (ref)
> 4	2.0 (1.5–2.8)	1.6 (1.4–1.8)	1.4 (1.2–1.7)	1.2 (0.9–1.6)
Lymph node metastases				
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	3.8 (3.0–4.9)	2.4 (1.8–3.2)	1.5 (0.9–2.7)	1.4 (0.5–3.5)

SEX STEROID HORMONES IN WOMEN

Regulation of sex steroid production

Sex steroid hormones – estrogens, progesterone and androgens – are synthesized in the ovary and in the adrenal cortex, but can also be converted in peripheral tissues, such as fat tissue [74], muscles [75], and the liver [76]. Hypothalamus is the central regulator of steroid hormone production through the hypothalamic-pituitary-ovarian (HPO) and hypothalamic-pituitary-adrenal axes.

The ovarian cycle

The HPO axis regulates the cyclic secretion of ovarian hormones during the ovarian/menstrual cycle. Gonadotropin releasing hormone (GnRH) from the hypothalamus stimulates the secretion of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. In turn, these gonadotropins control the secretion of sex steroid hormones from the ovaries [77].

During the early phase of the menstrual cycle (the follicular phase), circulating concentrations of FSH secreted by the pituitary gland increase and stimulate the growth and development of a group of follicles in the ovaries. Usually, only one of the follicles will be selected to fully mature and ultimately rupture at the time of ovulation. The growing follicle starts to produce estradiol and the peptide inhibin-B. In the ovulatory phase, the rise in estradiol and inhibin-B exerts positive feedback on LH secretion but inhibits FSH secretion from the pituitary. The LH surge stimulates the production of androgens and induces ovulation about 12 hours later. After ovulation, estradiol levels fall and the empty follicle in the ovary develops into the corpus luteum. During the later phase of the menstrual cycle (the luteal phase), the corpus luteum continues to produce estradiol and progesterone. In the absence of fertilization, the corpus luteum degenerates and the production of sex steroid hormones declines, which subsequently leads to the endometrial breakdown and menstruation [78].

The menopausal transition is the period in a woman's life when cyclic secretion of female sex hormones from the ovaries disappears. In contrast, circulating levels of androgens (i.e. testosterone) decline as a consequence of age-related reductions in secretion by both the adrenal glands and the ovaries [79]. Menopause, the final cessation of menstruation, occurs when functioning ovarian follicles become depleted and the production of estradiol is too low to stimulate the endometrium to grow and then shed. As a consequence of low estradiol production, circulating levels of FSH from the pituitary will increase. Menopause is established by a marked elevation of FSH in the blood [78]. The median age of menopause is 51-52 years in the Western world [80-82].

Ovarian sex steroid synthesis

Ovarian sex steroid synthesis takes place in follicular theca and granulosa cells, but also in the ovarian stroma. Cholesterol is the major precursor, originating from circulating lipoproteins or de novo synthesis in the ovary [77]. According to the Armstrong-Dorrington "two-cell theory" (Figure 3) [83], LH stimulates the theca cells to synthesize androgens. Androstenedione and testosterone diffuse into the granulosa cells, where FSH induces aromatase activity, and androgens are converted into estradiol, the major follicular product during the first half of the menstrual cycle. In late follicular phase, the granulosa cells of the corpus luteum are heavily vascularized, which allows cholesterol to enter directly. Cholesterol is converted to estradiol and progesterone, the major products of the corpus luteum during the second half of the menstrual cycle [77].

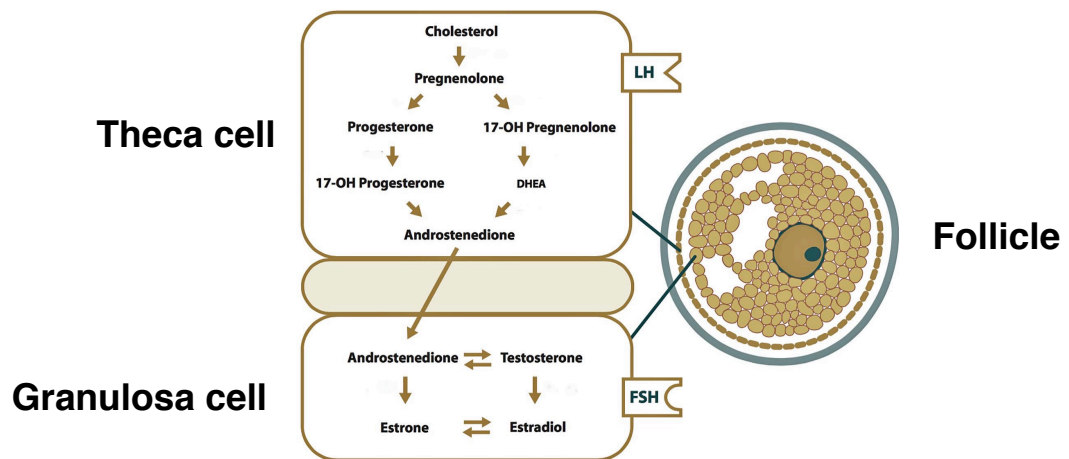


Figure 3. The "two-cell, two-gonadotropin theory" on ovarian steroidogenesis during the first half of the menstrual cycle. The pre-ovulatory follicle produces estradiol through a paracrine interaction between the theca and granulosa cells. In response to LH-stimulation, the theca cells convert cholesterol to androgens through several enzymatic steps. The granulosa cells do not have a direct connection to the circulation, but are dependent on diffusion of androgens (illustrated by androstenedione in the picture) from the theca cells as a substrate for estradiol aromatization. The aromatization is FSH-induced. Adapted from Schmidt [84], 2011 (illustration by Jan Funke), with permission.

Anti-Müllerian hormone (AMH)

Ovulation is not only regulated by the HPO-axis but also by a complex endocrine and paracrine signal-system of peptides [85] and growth factors in the oocyte, granulosa, theca, and stromal cells in the ovary [86]. A majority of these growth factors and signal molecules belong to the transforming growth factor (TGF- β) superfamily [87]. Anti-Müllerian hormone (AMH), previously called Müllerian inhibiting substance, is a dimeric glycoprotein [88] and a member of the TGF- β family. AMH is produced in the granulosa cells of the primary, pre-antral and small antral follicles (Figure 4) [89]. In these immature follicles, the paracrine activity of AMH inhibits FSH-stimulated follicle growth [78]. AMH concentration in these follicles remains high until the follicle reaches a diameter of about 8 mm, after which AMH production declines [90]. The decrease in AMH corresponds with the selection of a dominant follicle, which is characterized by the transition from low to high estradiol production [91]. AMH thereby regulates the development of the selected follicle that will undergo ovulation [92].

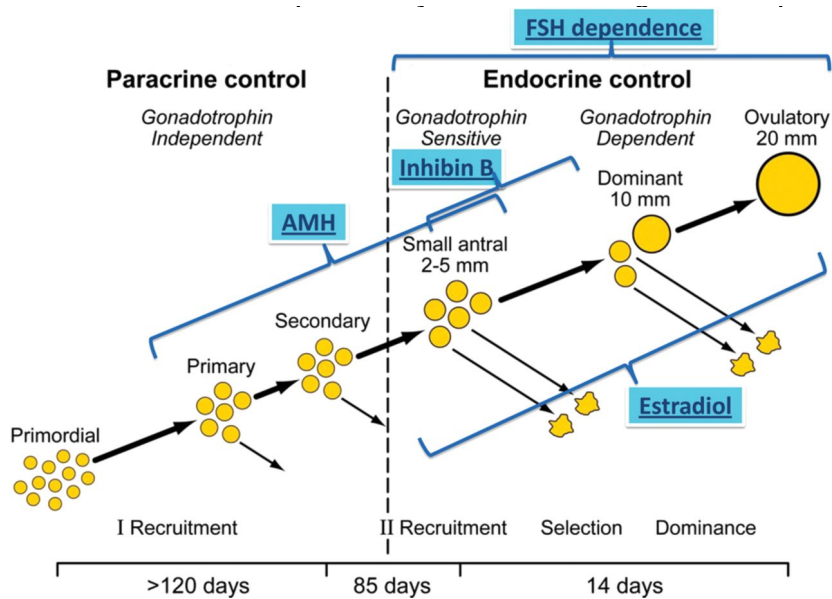


Figure 4. AMH is produced in early stages of follicle development (characterized by gonadotrophin-independent growth), as opposed to inhibin B and estradiol produced by follicles at later stages of development where growth is FSH-dependent. From Broer et al. [93], 2014, with permission.

Clinical use of AMH

Since serum AMH mainly derives from antral follicles, and antral follicles indirectly represent the total number of primordial follicles [94], serum levels of AMH can be considered a measure of the ovarian reserve [93]. Serum AMH is relatively stable throughout the menstrual cycle [95] and correlates well with antral follicle count [96]. AMH is therefore a better test of the ovarian reserve than serum levels of FSH, estradiol or inhibin B [93]. Clinically, serum AMH has mostly been used to predict ovarian response to hyperstimulation during in-vitro fertilization [97]. AMH production peaks at an age of about 25 years. Thereafter, there is a steady decline to undetectable levels at an average age of 50–51 years, corresponding to the menopause [98]. Therefore, individual AMH-values may predict time to menopause [99-106]. Serum AMH can be affected by ethnicity, smoking, and body mass index (BMI), but the results are not consistent [93]. Serum levels of AMH have been found to be lower in oral contraceptive users [107-110].

Measurement of AMH

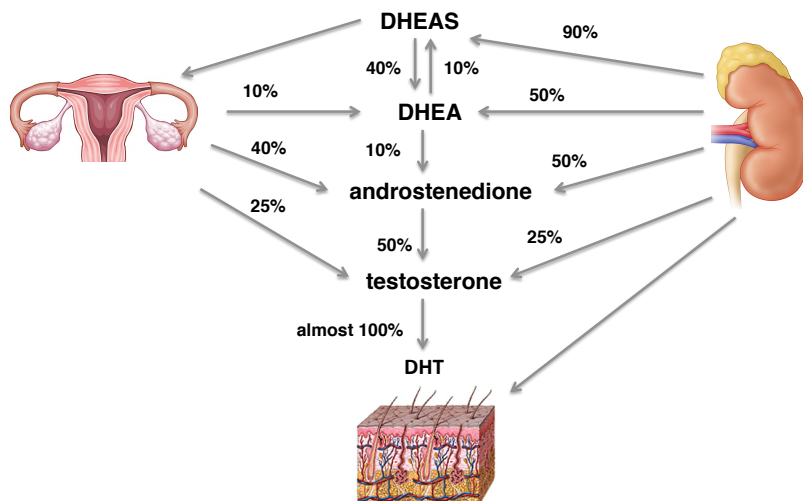
Serum AMH can be assessed by enzyme-linked immunosorbent assays (ELISA). In 2010, the AMH Gen II assay was introduced by Beckman-Coulter. This assay has a sensitivity of 0.08 $\mu\text{g/L}$ and lower inter- and intra-assay coefficient of variation (< 5%) compared to other assays, as well as no cross-reactivity to FSH, LH and inhibin [111]. However, the results may be affected by several other factors, for instance; pre-dilution, storage at -20°C for five days, and incubation at room temperature for seven days increased serum AMH concentrations [112]. Beckman-Coulter also issued a field safety notice warning that analysis of undiluted samples within 1-2 hours can generate higher values [113].

Female androgen production

In women, androgens are secreted by both the ovaries and by the adrenal glands. The major androgens produced in the ovary are androstenedione and testosterone. Androstenedione acts as a precursor for both estrogen and androgen synthesis and can be converted to testosterone and the more potent 5α -dihydrotestosterone (DHT) in the ovary [114] and in peripheral tissues (Figure 5) [115]. Testosterone and DHT are the two androgens that bind and activate the androgen receptor [77]. Since testosterone secretion is stimulated by LH, it has menstrual variation in fertile women, with a peak during the mid-cycle LH-surge [114]. Testosterone also displays circadian variation with peak levels in the early morning hours [79].

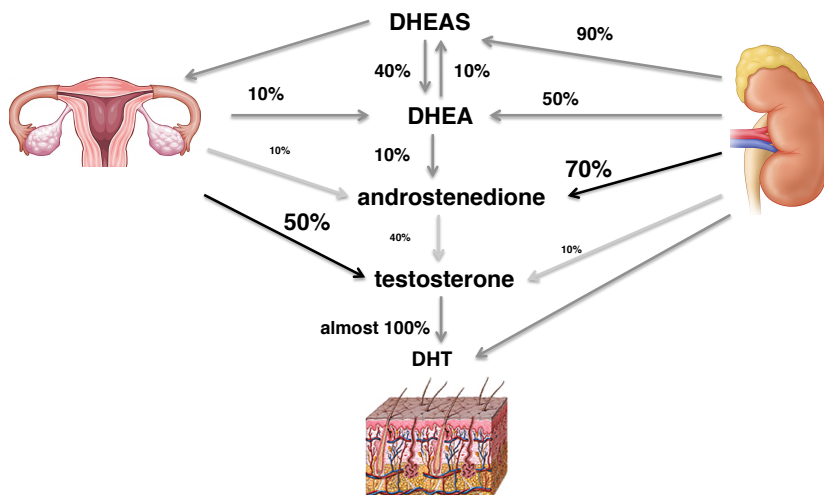
The adrenal gland produces dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, testosterone and small amounts of DHT [116]. Depending on availability of steroidogenic enzymes, DHEA and DHEAS can be peripherally converted to estradiol, testosterone and DHT [117]. In premenopausal women about half of circulating testosterone arises from direct secretion from the ovary and the adrenal gland of equal amount. The remaining half is produced from peripheral conversion of adrenal and ovarian androgens [118]. Serum testosterone levels decline steeply in the early reproductive years, but do not change drastically at menopause [119]. Ovarian testosterone production is considered to continue after menopause [79, 120]. The postmenopausal ovary produces less testosterone in absolute quantities compared to the premenopausal ovary, but proportionally more (about half) of the circulating testosterone [118, 121] (Figure 5).

Premenopausal women



In premenopausal women, androstenedione is secreted by the adrenal cortex (50%), the ovary (40%), and converted from DHEAS (10%). Testosterone is secreted by the adrenal cortex (25%) and the ovary (25%) with the remaining 50% being produced from circulating androstenedione.

Postmenopausal women



In postmenopausal women, androstenedione is secreted to a greater extent by the adrenal cortex (70%) compared to premenopausal women and to a lesser extent from the ovary (10%). Testosterone originates mainly from the ovary (50%) and to a lesser extent from circulating androstenedione (40%) and the adrenal cortex (10%).

Figure 5. Sources of androgens in premenopausal and postmenopausal women (percentages from Cameron et al. 2004 [116]). Dehydroepiandrosterone sulphate (DHEAS) is mainly a product of the adrenal cortex, and functions as a source of peripheral androgen production, for example in the ovary. Dehydroepiandrosterone (DHEA) is secreted by the adrenal cortex (50%) and the ovary (10%) and 40% is derived from circulating DHEAS. Dihydrotestosterone (DHT) is primarily a peripheral product of testosterone, but a small quantity is secreted directly by the adrenal gland.

Bioavailability and measurement of testosterone

Sex hormone-binding globulin (SHBG), produced in the liver, is a major determinant of the bioavailability of sex steroids. SHBG has a high affinity to both estradiol and testosterone. Around 65–70% of circulating testosterone is bound and inactivated by SHBG, 30–35% is loosely bound by albumin and only 0.5–3% represents freely circulating testosterone [122]. Since the binding of testosterone to albumin is rather weak, the free and albumin-bound fractions are defined as the bioavailable testosterone [123]. Oral estrogen is known to increase SHBG and thus lowering free testosterone, whereas androgens and progestin have the opposite effect [78].

The low concentration of free testosterone in female blood makes it difficult to obtain accurate measurements. Immunoassays are most commonly used in clinical practice, however, they are known for their inaccuracy due to cross-reactivity with other steroids and sensitivity to high levels of SHBG [123]. The most accurate method to assess total testosterone is liquid chromatography-tandem mass spectrometry (LC-MS/MS) [124]. Free testosterone can be calculated by equilibrium dialysis/ultrafiltration [123] or by the mass action equation based on total testosterone, SHBG and albumin concentrations [125]. The free androgen index (FAI) has been used as an approximation of free testosterone, and is calculated by dividing total testosterone concentration by SHBG concentration [126].

Free or bioavailable testosterone is traditionally considered the most reliable measure of tissue testosterone exposure [115] and the best determinant of overall clinical androgen status of women [127]. However, measurement of serum testosterone does not provide a specific measure of *total* tissue exposure or action [128]. In peripheral tissues, active steroids can be synthesized in the same cell as where their action is exerted, without release of the active steroids into the circulation [129]. The sensitivity of the androgen receptor differs between individuals, which may result in variability in end-organ response to circulating levels of androgens [115]. In summary, total androgenic action is determined by the level of androgens present in the circulation, the degree of binding to SHBG and albumin, the degree of inter-conversion to other androgens and estrogens, and the binding affinity of the androgen to the androgen receptor.

Biological effects of estrogens and androgens

Estradiol is the most potent estrogen and the dominant sex hormone in women. Estradiol initiates and completes epiphyseal closure during puberty [130], thickens the vaginal mucosa, enlarges the uterus, and promotes growth of ductal system of the breast [131]. In the liver, estrogens increase lipoprotein receptors, resulting in a decrease in serum concentrations of low-density lipoprotein cholesterol (LDL) [132]. Estrogens increase vasodilatation, promote angiogenic activity and inhibit apoptosis in endothelial cells [76]. Estrogens also cause increased coagulation activity [133].

Androgens are precursor hormones to estrogens, but they also act directly through the androgen receptor in numerous tissues in the body, including the brain [134]. Androgens have anabolic properties on bone and muscle and increase erythropoiesis [135]. Testosterone appears to affect mood, energy and sexuality in women, but the effects are less clear than in men [136]. Testosterone is thought to affect sexual arousal response in women [137]. Some studies have reported a correlation between higher endogenous androgen levels and better sexual function in women [138-153] whereas in other studies, no such correlation was found [128, 154-165] (Table 4).

Table 4. Studies on correlation between endogenous androgen levels and sexual function in women.

	Country	Study design	N of participants (age)	Androgens/s	Measurement of sexual function	Result
Persky, 1978 [138]	USA	Cohort	11 (21-31 years)	TT	Interview	Midcycle TT correlated with intercourse frequency
Bancroft, 1980 [154]	UK	Case-control	20 OC users with sexual problems and 20 controls (19-36 years)	TT, FT, A	Interview, diary	No difference between cases and controls
Persky, 1982 [139]	USA	Cross-sectional	30 (21-60 years)	TT, A, DHEA, DHT	SII, CCR, CI, L-W MAS	Higher A and T correlated with sexual desire, all androgens correlated with intercourse frequency and sexual gratification
Bachmann, 1984 [155]	USA	Cross-sectional	69 (50-65 years)	TT, A	Interview	No correlation
McCoy, 1985 [140]	USA	Cohort	16 (perimenopausal age)	TT	Diary, interview	Higher TT correlated with coital frequency
Alder [141], 1986	UK	Cohort	25 (20-38 years)	TT, A	Diary, interview	Women with reduced sexual interest had significantly lower A and TT
Morris, 1987 [142]	USA	Cohort	43 (21-34 years)	TT, FT	Diary	Higher midcycle TT and FT correlated with coital frequency
Stuart [156], 1987	USA	Case-control	59 with ISD and 31 non-ISD (mean age 33 years)	TT	Case records	No difference between groups
Schreiner-Engel, 1989 [157]	Italy	Case-control	17 with HSD (27-39 years) 13 controls (26-45 years)	TT, FT	Interview (DSM III)	No difference between cases and controls
Bachmann, 1991 [143]	USA	Cross-sectional	59 (60-70 years)	TT, FT	Interview, L-W MAS	Higher FT correlated with sexual desire
Alexander, 1993 [144]	Canada	Cohort	19 OC users (18-35 years)	FT	Study-specific questionnaire, diary, dichotic listening task	Higher FT correlated with sexual desire and activity
Nathorst-Böös, 1993 [166]	Sweden	Cross-sectional	101 (52±2 years)	TT, FT, A, DHEAS	MSFQ	No correlation
Van Goozen, 1997 [145]	Netherlands	Cohort	19 (24-40 years)	TT, FT, A, DHEAS	Diary	FT correlated with sexual interest, intercourse frequency, and orgasm, TT, A, and DHEAS correlated with masturbation

Table 4 continued

	Country	Study design	N of participants (age)	Androgen/s	Measurement of sexual function	Result
Flöter, 1997 [167]	Sweden	Cross-sectional	83 (40-53 years)	T, FAI, A, DHEAS	MSFQ	Androgens correlated with sexual function scores in women without HT
Riley, 2000 [146]	UK	Case-control	15 women with sexual drive disorder (18-45 years) and 15 controls	TT, FT, DHT	Diary, BISF-W, HISS, HISE	FT was lower among cases
Greendale [158], 2001	USA	Cross-sectional	61 postmenopausal breast cancer survivors (43-70 years)	TT, FT, DHEAS	CARES, Schover and Jensen's Sexual History Form	Higher FT correlated with less sexual interest
Dennerstein, 2002 [159]	Australia	Cohort	226 (45-55 years)	TT, FT, DHEAS	SPEQ	No correlation between androgens and declining SPEQ scores during menopause
Guay, 2002 [147]	USA	Case series	105 women with decreased sexual desire (24-78 years)	TT, FT, DHEAS	Patient reported	70% had lower TT, FT and DHEAS than the general population
Gracia, 2004 [160]	USA	Cohort	326 (35-47 years)	TT, DHEAS	Study-specific questionnaire	TT fluctuating over time was associated with decreased libido
Guay, 2004 [148]	USA	Case-control	18 cases with FSD (20-49 years) and 14 controls	TT, FT, A, DHEAS	AFSQ	T and adrenal androgen precursors were lower in cases
Dennerstein, 2005 [161]	Australia	Cohort	336 (45-55 years)	TT, FAI, DHEAS	SPEQ	Androgens were not predictive of sexual function during/after menopause
Davis, 2005 [128]	Australia	Cross-sectional	1423 (18-75 years)	TT, FT, A, DHEAS.	PFSF	No correlation
Turna, 2005 [149]	Turkey	Case-control	40 women with low libido (24-70 years) and 40 controls	TT, FT, DHEAS	FSFI	TT, FT and DHEAS were lower among women with low libido
Santoro, 2005 [150]	USA	Cross-sectional	2961 (40-55 years)	TT, FT, DHEAS	Study-specific questionnaire	Higher TT was weakly associated with sexual desire
Aziz [162], 2005	Sweden	Cohort	217 before/after hysterectomy (48±2 years), 106 before/after hysterectomy and SOE (50±2 years)	TT, FAI, A, DHEAS	MFSQ	No correlation between reduced androgen levels and sexual function
Speer [163], 2005	USA	Cross-sectional	55 breast cancer survivors (40-69 years)	TT, FT	FSFI	No correlation
Galicchio, 2007 [151]	USA	Cross-sectional	441 (45-54 years)	TT, FT, A, DHEAS	Study-specific questionnaire	Higher TT and FT was associated with desire to have more frequent sexual relations

Table 4 continued

	Country	Study design	N of participants (age)	Androgen/s	Measurement of sexual function	Result
Alder [164], 2008	Switzerland	Cross-sectional	29 women with breast cancer (47±6 years)	TT, A, DHT, DHEA, DHEAS,	FSFI, Relationship Questionnaire	No correlation
Basson, 2010 [165]	USA	Case-control	121 women with HSDD, 124 controls (>35 years)	A, DHT, DHEA, DHEAS	SIDI, Detailed Assessment of Sexual Arousement	Lower levels of precursor androgens, but not androgens or their metabolite, were found in cases
Alarslan, 2011 [152]	Turkey	Cross-sectional	118 (42-67 years)	TT, FT, A	FSFI	TT was lower in women with sexual dysfunction
Wahlin-Jacobsen, 2014 [153]	Denmark	Cross-sectional	560 (19-65 years)	TT, FT, A, DHEAS	FSFI	Higher FT and A correlated with sexual desire
Caruso, 2014 [168]	Italy	Cohort	1180 (18-40 years) without sexual dysfunction	TT, FAI	FSFI	Correlation between sexual activity and androgenic hormones

HSDD and HSD, hypoactive sexual desire; ISD, inhibited sexual desire; TT, total testosterone; FT, free testosterone; FAI, free androgen index; A, androstenedione; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosteronesulphate; DHT, dihydrotestosterone; PFSF, Profile of Female Sexual Function; FSFI, Female Sexual Function Index; L-W MAS, Locke-Wallace Marital Adjustment Scale; BISF-W, Brief Index of Sexual Functioning for Women; HISS, Hurlbert Index of Sexual Desire; HISE, Hurlbert Index of Sexual Excitability; SII, LoPiccolo-Steger Sexual Interaction Inventory; CCR, Couple Compatibility Ratio; CI, Couple Interaction Score; AFSQ, Abbreviated Sexual Function Questionnaire; SPEQ, Short Personal Experiences Questionnaire; SIDI, Sexual Interest and Desire Inventory; CARES, Cancer Rehabilitation Evaluation System; MSFQ, McCoy Female Sex Questionnaire; SDI, Sexual Desire Inventory; GWB, General Wellbeing Index

SIDE-EFFECTS OF CERVICAL CANCER TREATMENT

Since cervical cancer has high overall survival rates among women in young ages, treatment-related morbidity is an important aspect of cervical cancer survivorship. Issues of special concern to women with cervical cancer include threats to body image, sexuality and reproduction [169]. Surgical treatment can consist of removal of the uterus and ovaries, leading to permanent loss of fertility. Radiotherapy in premenopausal women is associated with onset of menopause. Chronic side effects can develop either directly from acute toxicities, or come years after completed cancer treatment.

Side-effects of cancer treatment on ovarian function

In toxicology, the median lethal dose (LD_{50}) of a toxin or radiation is the dose required to kill half the members of a tested population. The LD_{50} for the human oocyte has been determined to be < 2 Gy [170]. When external beam radiotherapy is given, the total dose to the ovaries usually exceeds 45 Gy, thus resulting in destruction of the oocytes and complete cessation of estrogen production. In premenopausal women, this causes a sudden onset of menopause. Symptoms from iatrogenic menopause can include vasomotor symptoms, vaginal dryness, urinary incontinence and urinary tract infections, insomnia, mood changes, and loss of libido [171].

Iatrogenic menopause can also be caused by salpingo-oophorectomy (SOE), which is performed if there is a risk of tumor spread to the ovaries. However, there are also indications that hysterectomy alone can adversely affect ovarian function and shorten the time to menopause, even if the ovaries are not removed [172]. Reduction of the ovarian reserve after hysterectomy as measured by serum levels of FSH [173-178] and inhibin B [176] has been described. One study reported earlier ovarian failure in women having vaginal hysterectomy, but not following abdominal hysterectomy [179]. On the other hand, some investigators found no association between hysterectomy and age of menopause [180, 181], or levels of FSH [182].

Circulating FSH rises in response to reduced inhibin and estrogen secretion from the ovarian follicles in the years before the menopause. However, single FSH measurements have limited ability to predict reproductive status, and no specific concentration of inhibin B has been shown to be diagnostically discriminatory [183]. Serum AMH has therefore gained increasing attention as a marker of reproductive ageing.

Reduction of ovarian reserve measured by AMH in cancer patients

Serum AMH has been used as an assessment of damage to the ovarian follicle reserve due to various cancer treatments [184]. However, the effect of radiotherapy alone, or in combination with cisplatin, as treatment for cervical cancer has not been evaluated by AMH measurements. Among women treated with alkylating agents or pelvic or total body irradiation in childhood, serum levels of AMH are generally very low [185, 186]. Cisplatin is considered to have moderate gonadotoxic effects [187], and since the radiotherapy alone already has a detrimental effect on the ovarian follicles, it is unlikely the cisplatin has any additional effect. The effect of cisplatin alone, or in combination with topotecan or paclitaxel, has not been examined.

The effect of radical hysterectomy on serum AMH-levels has not been investigated previously. Following simple hysterectomy (Table 5), a decline in AMH has been reported after 1 [188], 3 [189] and 4 [188, 190] months. Muraji et al. [191] compared AMH levels cross-sectionally and found lower values among previously hysterectomised women versus comparators. Other investigators did not find any decrease in serum AMH 3 months after laparoscopic [192-194] or abdominal [195] hysterectomy, or 2 years after any type of hysterectomy [196]. There is thus no consensus regarding effects of hysterectomy on serum AMH levels, and most studies have been small. In the largest study with 158 patients, no change in serum AMH was found [194].

Table 5. Studies on serum levels of anti-Müllerian hormone (AMH) levels following hysterectomy.

	Study design	Result
Hehenkamp [196], 2007	AMH before and 6 weeks, 6, 12, 18 and 24 months after uterine artery embolization (n=30) and hysterectomy (n=33)	AMH decreased after uterine artery embolization, but not after hysterectomy in relation to the normal decline due to aging.
Lee [192], 2010	AMH before, 1 week, 1 month and 3 months after laparoscopy-assisted vaginal hysterectomy (n=26) and abdominal hysterectomy (n=6)	No change in AMH
Atabekoglu [190], 2012	AMH before and 4 months after hysterectomy (n=22) and comparators without hysterectomy (n=20)	AMH decreased in both groups
Muraji [191], 2012	Cross-sectional measurement of AMH > 2 years after trachelectomy (n=18) and hysterectomy (n=16) versus comparators (n=10,186)	AMH levels in the hysterectomy group were lower than in the trachelectomy and comparison group.
Wang [189], 2013	AMH before, 2 days and 3 months after laparoscopy-assisted vaginal hysterectomy (n=10), abdominal hysterectomy (n=25) and myomectomy (n=35)	AMH was lower 2 days and 3 months after hysterectomy, but for myomectomy AMH was only lower at 2 days
Findley [193], 2013	AMH before, 4-6 weeks and 3 months after laparoscopic hysterectomy with (n=14) or without (n=13) bilateral salpingectomy	AMH was not decreased at 3 months compared to baseline in either treatment groups.
Morelli [194], 2013*	AMH before and 3 months after laparoscopic hysterectomy with (n=79) or without (n=79) bilateral salpingectomy	No decrease in AMH after hysterectomy with or without salpingectomy
Gökgözoğlu [195], 2014	AMH before, 1 and 3 months after hysterectomy (n=29)	AMH decreased from baseline to 1 month, but was not different from baseline at 3 months
Yuan [188], 2015	AMH before, 1 and 4 months after total laparoscopic (n=33) or supracervical (n=34) hysterectomy	AMH decreased after hysterectomy, with a greater decrease after total hysterectomy.

* Gen II Elisa assay kit

Treatment effects on serum androgens

The effects of radiotherapy on ovarian androgen production are not well known. In a study from 1981, Janson et al. measured testosterone levels in serum among 14 premenopausal women undergoing radiotherapy (45 Gy) and found no reduction [197]. Inskip et al [198], 1994, measured serum testosterone and androstenedione in 9 pre- and postmenopausal women before and 4-12 months after radiotherapy (50 Gy) and found reduced levels only in the postmenopausal women (n=4).

The ovarian stroma, where much testosterone synthesis takes place, seems to be more resistant to radiotherapy than the follicular tissue [198]. It is not known at which critical dose level androgen production from the ovaries is suppressed, but based on animal and human in vitro experiments it has been hypothesized to be at approximately 5-6 Gy [199]. A radiation effect on adrenal hormone production has been suggested [200], but has not been confirmed [198].

The effect of chemotherapy treatment for cervical cancer (alone or in combination with radiotherapy) on androgen levels has not been examined.

Bilateral SOE eliminates all ovarian sources of androgens, and SOE has been associated with a 15-50% decline in serum testosterone [120, 162, 201-203]. Cross-sectional studies among postmenopausal women showed that women with previous SOE had lower testosterone than non-oophorectomised women [119, 204-208].

Aziz et al. [162], examined perimenopausal women before and one year after hysterectomy with ovarian conservation, and found a 15% reduction of FAI, but no change in total testosterone. Cross-sectional studies have found lower levels of total [204, 207, 208] and free [204, 207] testosterone among hysterectomised women compared to women after natural menopause.

Table 6 summarizes measurements of serum androgens following radiotherapy and hysterectomy with or without SOE. The effects of radiotherapy on androgen levels are practically unknown [198]. Bilateral SOE seems to reduce testosterone up to 50% [120, 162, 201-203, 209], but smaller studies (n≤15) [120, 201, 203] and imprecise measurement methods [120, 162, 201, 202, 209] are limitations, and the use of hormone therapy (HT) [162] may have biased the results. Cross-sectional studies indicate that hysterectomised women have slightly lower testosterone levels than women after natural menopause [204, 207, 208], but prospective studies are mostly missing [162].

Table 6. Studies on the effects of radiotherapy, hysterectomy with SOE and hysterectomy without SOE on female androgen levels.

Study design		Result
Radiotherapy		
Janson [197], 1981	Cohort study, before and 6-8 weeks after brachytherapy (premenopausal N=14)	No decline in TT
Inskip [198], 1994	Cross sectional, by menopausal stage, SOE and radiotherapy (N=147) Cohort, before and after radiotherapy (premenopausal n=5, postmenopausal n=4)	Compared to hysterectomy alone, androstenedione was lower after radiotherapy in premenopausal women, and TT was lower after SOE +/- radiotherapy in postmenopausal women. Cohort: decline in TT only in postmenopausal women
Oophorectomy		
Judd [202], 1974	Cohort study, before and 6-8 weeks after SOE (premenopausal n=5, postmenopausal n=16)	Decline in TT and androstenedione in both groups
Chakravarti [210], 1977	Cross-sectional, 0-31 years after SOE (N=100)	Lower TT only during the first year after surgery compared to mean values from women after natural menopause
Vermuelen [205], 1980	Cross-sectional, previous SOE (n=15) versus natural menopause (n=70)	Lower T, but not androstenedione
Hughes [201], 1991	Cohort study, before and 6 weeks after SOE (premenopausal n=4, postmenopausal n=11)	Both groups: 50% reduction of TT and androstenedione, no reduction of DHEAS
Nathorst-Böös [166], 1993	Cross-sectional, previous SOE without HT (n=33), previous SOE with HT (n=33), hysterectomy without SOE (n=35)	Higher TT and FT in women with preserved ovaries compared to women with previous SOE and HT
Sluijmer [209], 1995	Cohort study, 2 weeks before and 6 weeks after SOE (postmenopausal with GnRH-agonist n=15, without GnRH-agonist n=20)	Lower TT, but not androstenedione and SHBG, in both groups
Laughlin [204], 2000	Cross-sectional, previous SOE (n=123) vs no surgery (n=438)	40% lower TT and FT, 10% lower androstenedione
Davison [119], 2005	Cross-sectional, previous SOE (n=27) vs no SOE (n=183)	Lower TT and FT, but not androstenedione or DHEAS
Aziz [162], 2005	Cohort study, perimenopausal women before and one year after SOE (n=101)	Lower TT, FAI, androstenedione and DHEAS
Cappola [206], 2007	Cross-sectional, previous SOE (n=56) vs no or unilateral SOE (n=291)	23% lower TT, 16% lower FT
Fogle [120], 2007	Cohort study, before and 55 +/-39 days after SOE (postmenopausal N=13)	42% lower TT postoperatively
Alarslan [152], 2011	Cross-sectional, previous SOE (n=35) vs natural menopause (n=83)	No difference in androstenedione, TT, FT, DHEAS

Table 6 continued

	Study design	Result
Bui [203], 2010	Cohort study, 1-2 years before and after SOE (n=8) vs natural menopause (n=16)	45% lower TT after SOE, no difference after natural menopause
Key [207], 2011	Cross-sectional re-analysis of 13 studies, SOE (n=315) vs natural menopause (n=3685)	13% lower androstenedione, 11% lower DHEAS, 30% lower TT and FT
Kotsopoulos [208], 2015	Cross-sectional, SOE (n=163) vs natural menopause (n=1090)	Lower DHEAS and TT
Hysterectomy		
Laughlin [204], 2000	Cross-sectional, hysterectomy with no or unilateral SOE (n=123) vs no surgery (n=438)	10% lower androstenedione, 29% lower TT and FT
Aziz [162], 2005	Cohort study, perimenopausal women before and one year after hysterectomy (n=206)	Lower androstenedione and FAI
Key [207], 2011	Cross-sectional re-analysis of 13 studies, hysterectomy (n=603) vs natural menopause (n=3685)	5% lower androstenedione, 10% lower DHEAS, 15% lower TT and FT
Kotsopoulos [208], 2015	Cross-sectional, hysterectomy (n=191) vs natural menopause (n=1090)	Lower DHEAS and TT

SOE, salpingo-oophorectomy; TT, total testosterone; FT, free testosterone; FAI, free androgen index; HT, hormone therapy

Sexual dysfunction after cervical cancer treatment

Sexual dysfunction is one of the most disturbing sequelae after treatment of cervical cancer [211, 212]. Several researchers [213-216] have tried to compile results from previous studies, which is difficult due to the use of different study designs and methods of evaluating sexual function. In questionnaire-based assessments, women have reported varying degrees of vaginal dryness [211, 217-223], dyspareunia [219, 220, 222, 224, 225], short vagina [211, 220, 222] and sexual dissatisfaction [218, 222].

The pathophysiology of sexual dysfunction after cervical cancer treatment has several possible explanations, including both physical and psychological factors. Radical hysterectomy can result in vaginal fibrosis [215], and damage to the autonomic nerves [226], causing a reduction in vaginal blood flow and reduced lubrication [227]. Decreased blood flow and fibrosis can also occur as a consequence of radiotherapy [228]. Estrogen deprivation following radiotherapy or SOE leads to atrophy of the genital organs and diminished vaginal lubrication [229].

Androgen deficiency as a cause for sexual dysfunction

Testosterone is important for the maintenance of musculoskeletal health and brain function in women [230], but it is in the treatment of hypoactive sexual desire disorder (HSDD) that testosterone has attracted the most attention [231]. HSDD is defined as deficiency of sexual desire causing personal distress [232]. In 2002, the term female androgen insufficiency syndrome (FAIS) was used as a definition for decreased libido and wellbeing, persistent fatigue, bone loss and decreased muscle mass in the presence of low levels of bioavailable testosterone and normal estrogen status [127]. The term FAIS is, however, not used today due to the lack of correlations between specific androgen levels and symptoms [233, 234]. The prevalence of low sexual desire has been reported high – 33% – among Swedish women, but the prevalence of sexual problems associated with personal distress was 14% [235] (12% in the US [236]).

It is difficult to correlate endogenous androgen levels to sexual function (Table 4), and considering publication bias and lack of consistency in the findings, probably no such simple association exists in healthy women. However, randomized studies with testosterone therapy have shown improvements in outcome measures such as sexual activity, desire, wellbeing, and reduced distress [237-242]. A Cochrane analysis concluded that testosterone treatment in addition to standard HT can improve sexual function in postmenopausal women with self-reported low libido [243]. Testosterone therapy in women has not been found to have adverse effects on cardiovascular disease, endometrium [244] or breast [245]. Therefore testosterone can be used to treat HSDD [246].

Associations between androgen levels and sexual dysfunction among cervical cancer survivors have not been examined. Among breast cancer survivors, Alder et al [164] examined 29 premenopausal women. The only two factors that were associated with sexual function were relationship quality and the use of chemotherapy, not androgens or their metabolites. Speer et al. [163] investigated sexual function in 55 breast cancer survivors. No correlation was found between hormonal levels and sexual functioning. In that study, depression and having traditional role preferences were the most important determinants of low sexual desire. Greendale et al. [158] investigated 61 postmenopausal breast cancer survivors and found that higher levels of bioavailable testosterone were associated with less sexual interest.

The use of testosterone therapy among female cancer survivors has only been examined in one randomized controlled trial [247] comparing transdermal testosterone and placebo for the improvement of sexual desire in 150 female survivors of mixed cancers who were not using estrogen supplements. Serum levels of bioavailable testosterone increased in the intervention group, but there were no group differences in sexuality scores from before to after treatment, perhaps because the women were also estrogen deprived.

Morbidity associated with early menopause

The term premature ovarian failure, or premature ovarian insufficiency (POI), refers to menopause before 40 years [248]. Early menopause refers to menopause at 45 years or younger [249]. Spontaneous premature ovarian insufficiency affects approximately 1% of all women [248] and is usually idiopathic, but can also be caused by autoimmune disorders, genetic causes, infections or inflammatory conditions, enzyme deficiencies, or metabolic syndromes [250]. Iatrogenic early or premature menopause can be induced by radiotherapy or chemotherapy as cancer treatment, or by surgical treatment (bilateral SOE) [81].

Early menopause is associated with osteoporosis and increased fracture risk [251, 252], coronary heart disease [253-256], stroke [255-257], cognitive impairment [258], cardiovascular mortality [254, 259-263], and total mortality [254, 261, 264-266]. Among women undergoing bilateral SOE, cardiovascular mortality [262, 263] and all-cause mortality [266] have been reported to be higher among women not taking estrogen after surgery. Endothelial dysfunction has been suggested to contribute to the increased risk of cardiovascular disease and mortality in women with POI. In one study, HT restored endothelial function within 6 months of treatment [267].

Hormone therapy (HT) for women with natural and early menopause

Exogenous estrogens are used as HT among healthy women for menopausal symptoms, such as hot flashes. HT also reduces postmenopausal vaginal dryness, improves sexual function [268] and reduces the risk of osteoporotic fractures [269]. However, long-term use of combined continuous HT (estrogen plus progestin) in older postmenopausal women increases the risk of coronary heart disease, venous thromboembolism, stroke, breast cancer, gallbladder disease, dementia, and death from lung cancer [269]. Following reports of negative effects of HT, for instance from the famous Women's Health Initiative trial [270], HT use has decreased among women 50-59 years of age [271]. Importantly, age and time since menopause seems to influence the risk/benefit associated with HT. This concept is called the *timing or window of opportunity* hypothesis [272, 273]. Thus, in women starting the treatment less than 10 years since menopause, HT use is associated with *decreased* risk of coronary heart disease and *reduced* overall mortality rate despite a small increased risk of breast cancer after longer use [274].

The potential risks associated with postmenopausal HT do not at all apply to women with early or premature menopause [275]. HT in these women has been shown to counteract loss of bone mass [276] and decrease the risk of cardiovascular death [262]. Furthermore, women with early menopause already have a decreased risk of breast cancer [277], which does not increase with HT [278].

In light of the above, HT is recommended for women with premature or early ovarian insufficiency to reduce morbidity and mortality, and should be used at least until the average age of natural menopause. Contraindications to HT among women in early menopause are the same as for perimenopausal women [279], i.e. hormone-dependent tumor, undiagnosed genital bleeding or endometrial hyperplasia, untreated hypertension, arterial or venous thromboembolic disease, porphyria cutanea tarda, and active liver disease [280]. Estrogen doses should be high enough to achieve serum levels within physiological levels of fertile-aged women [281]. Therefore, women with early menopause may need higher estrogen doses than women who use HT to relieve symptoms after natural menopause [82].

Hormone therapy in cervical cancer survivors

Squamous cell cancer, which is the most common histopathological type of cervical cancer, is not considered to be an estrogen-responsive disease [29], and HT after treatment of squamous cell cancer is uncontroversial [282-286]. On the contrary, for adenocarcinoma, the safety of HT use among survivors has been questioned, based on reports of an association between HT use and cervical adenocarcinoma [28, 29].

In a population-based study by Jaakkola et al. [29], a decreased risk of squamous cell cancer (standardized incidence ratio (SIR) 0.34, 95% confidence interval (CI) 0.16-0.65), but an increased risk of adenocarcinoma (SIR 1.83, 95% CI 1.24-2.59), was found in association with 5 years of HT-use. In absolute numbers, among 10,000 women followed for 10 years who used HT > 5 years, these association translated to 2-3 fewer cases of cervical squamous cell carcinoma, but 2 more cases of adenocarcinoma than among average Finnish women. Lacey et al. [28] conducted a case– control study of 124 women with adenocarcinomas, 139 women with squamous cell carcinomas, and 307 matched controls. No significant associations were found for ever-use of HT, but unopposed estrogens were positively associated with adenocarcinomas (odds ratio (OR) 2.7, 95% CI 1.1-6.8).

Several other studies have not shown increased risk of cervical cancer in general in association with HT use [287-290], however in these studies no distinctions were made between adenocarcinoma and squamous cell cancer. Only one study has investigated the safety of HT after cervical cancer treatment. Ploch et al. prospectively compared 80 women with HT and 40 comparators following surgery or radiotherapy for stage I or II cervical cancer over a period of 5 years [291]. They found no difference in disease recurrence or overall survival between the two groups. According to present knowledge, there is no evidence to suggest that HT cannot be safely administered to cervical cancer survivors up to age of natural menopause [171, 291, 292].

Cardiovascular disease

Due to the associations between early menopause and cardiovascular disease [253-257, 259-263], in addition to the well-established associations between smoking and cervical cancer [32], and smoking and cardiovascular disease [293], cervical cancer patients would be expected to be at increased risk of cardiovascular disease. However, the few studies on this topic have shown diverging results. The risk of stroke was found increased (5-year cumulative risk: 8% vs 5%) [294], decreased (adjusted hazard ratio (HR) 0.58, 95% CI 0.54-0.61) [295] or with no difference versus the general population [296]. For ischemic heart disease, previous results are also contradictory. The risk of myocardial infarction was found doubled after SOE, but not significantly increased after radiotherapy in a study by Hsieh et al. [297]. Maduro et al. [296] and Tsai et al. [294] both found increased risks of myocardial infarction among cervical cancer patients (doubled versus the general population and 60% higher risk versus comparators). In Sun et al. [298], cervical cancer patients were found to have a 43% lower risk of ischemic heart disease (defined as 3 diagnoses of ICD9 410 to 414). However, the decreased risk was mainly found in patients above 50 years of age, and in those with a follow-up of 3 years or less. The use of HT was also investigated in that study [298], and HT use was associated with a lower risk of ischemic heart disease among cervical cancer patients using HT versus cancer-free comparators not on HT.

Fragility fractures

Menopause increases the risk of osteoporosis and fracture due to a decrease in serum estradiol, but can also be mediated by decreased levels of androgens [299]. Estradiol inhibits bone turnover by binding to estrogen receptors on osteoblasts and osteoclasts [300]. Androgen action on bone depends on aromatization of androgens into estrogens, but can also be directly mediated [301]. The mechanisms by which radiotherapy affects bone are likely a combination of direct cellular effects and vascular ischemia [302]. The 2 to 5-year cumulative incidences of pelvic insufficiency fractures among women treated with external beam radiotherapy have been reported to be 5-45% [302-307] (but with no comparison group). In most studies, high age [302-304, 306] and low body weight [303-306] have been reported as additional risk factors.

Secondary cancers

Several large studies have reported cervical cancer survivors to be at increased risk of developing secondary cancers [308-311], with around 30% more cancer cases overall than in the population. Patients treated with radiotherapy developed cancers at heavily irradiated sites (colon, rectum/anus, urinary bladder, genitals) [308, 311] consistent with a radiation etiology, but patients who did not receive radiotherapy also had an increased risk of cancer of pharynx, genitals, and rectum/anus, suggesting a HPV etiology [308, 310]. The incidences of cancers related to smoking, including cancers of the urinary bladder, lung and bronchus were also increased [308, 310, 311].

Quality of life in cervical cancer survivors

Health-related quality of life (QoL) is usually assessed by patient questionnaires, which can be generic (i.e. could be used in any population) or disease-specific. Four questionnaires have been validated among cervical cancer survivors: The European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24 [312, 313], the Female Sexual Function Index (FSFI)[314], the Leiden Questionnaire [315], and the Sexual Function-Vaginal Changes Questionnaire [316]. The FSFI [317] and EORTC QLQ-CX24 [312] have validated Swedish versions.

Two systematic reviews have evaluated studies on different dimensions of QoL among cervical cancer survivors [214, 216]. Both indicate difficulties in comparing results from different studies and drawing general conclusions, due to the variety of questionnaires used and heterogeneity of participants. Findings regarding physical and psychosocial wellbeing vary considerably, while findings concerning sexuality are more consistent [214].

Most studies have shown that QoL in cervical cancer survivors is reduced compared with the general population. Apart from sexual dysfunction (described earlier), impaired anorectal and gastrointestinal function, urinary symptoms, and lymphedema are the most commonly reported distressful symptoms [214, 216].

Gastrointestinal morbidity

Bowel dysfunction stems from surgical damage to the lumbosacral nerve plexus [318, 319], postoperative adhesions [320] or as a consequence of radiotherapy. Radiotherapy causes gastrointestinal mucosal inflammation and can lead to ischemia and fibrosis [321], chronic proctitis or enteritis, bile acid malabsorption and bacterial overgrowth [322]. Constipation [323], tenesmus [217], diarrhea [222, 323-326], and fecal incontinence [318] are patient-reported symptoms, associated with much distress [212].

Urologic morbidity

Lower urinary tract dysfunction after radical hysterectomy can occur as a consequence of surgical damage to the pelvic nerve plexa when resecting the cardinal ligaments and sacrouterine ligaments. Damage to the parasympathetic nerves results in a hypocontractile bladder with decreased sensation, whereas damage to the sympathetic system leads to reduced bladder compliance, increased storage pressure and bladder neck incompetence, resulting in urinary incontinence [327]. Radiotherapy can cause microvascular damage, inflammation and fibrosis. Late urological complications to radiotherapy are cystitis, ureteric stenosis, fibrotic shrunken low-compliance bladder, and fistula formation [328]. Urinary symptoms are frequent following both surgery and radiotherapy and include incontinence (33-53%) [216, 217] as well as voiding dysfunction (53-81%) [216, 217, 329]. Among long-term survivors (5 to 15 years), women treated with radiotherapy were more affected by voiding problems [330].

Lymphedema

Radical hysterectomy includes removal of the external iliac, internal iliac and obturator lymph nodes, thus disrupting the lymph drainage routes. Secondary lymphedema of the legs and genital area is a common side effect due to the accumulation of lymph in the subcutaneous fat, leading to edema, chronic inflammation and fibrosis. Patients may present with varying degrees of severity, from mild swelling to large edematous enlargement. Lymphedema is one of the most disabling symptoms [211, 331] and unlike other symptoms, may worsen over time [325, 330, 332]. The prevalence of lymphedema has been reported 2-26% [329, 333-338] with a higher prevalence after radical hysterectomy in combination with radiotherapy [212, 330, 334, 337, 338].

Psychological wellbeing

Compared to the general population, long-term cervical cancer survivors had more mental fatigue and anxiety in a study by Le Borgne et al. [330]. Mantegna et al. [331], found an improvement over time regarding emotional distress, but elevated anxiety levels were still present 2 years after treatments in approximately 12% of early-stage and in 16% of locally advanced relapse-free cervical cancer patients (no comparison group). Conflicting results were reported by Kim et al. [339], who investigated 828 cervical cancer survivors (mean time since diagnosis 7 years) and who found that anxiety scores did not differ from those of healthy comparators and that depression scores were lower. Among young (21-49 years old) survivors of mixed gynecological cancers, 63/88 women reported distress in relation to loss of, or impaired fertility, and their levels of distress and depression were associated with the severity and number of menopausal symptoms [340].

Work loss and cancer

A challenge of treating cancer is not only to find efficient therapies for the disease, but also to minimize medical and social hazards [341]. The ability to work following cancer treatment is important for maintaining self-esteem, identity, and living conditions. It is also important for society to keep people employed for economic reasons and to prevent social inequity [342]. Investigations on work loss among cancer patients therefore involve aspects of cancer care and rehabilitation.

Studies on cancer patients in general have reported return-to-work rates of 24-94% [343, 344] increasing with time from cancer diagnosis. Nevertheless, some patients suffer from health problems, which lead to partial or total work disability [345]. A meta-analysis showed that cancer survivors overall were more likely to be unemployed than healthy comparators: 34% versus 15% [346]. Cancer patients do not differ from the population in that higher education and better social climate at work is associated with better work ability and that old age and co-morbidity reduce work ability [347]. However, other individual and treatment-related factors also influence work disability in cancer survivors [343, 344, 348-351], and therefore results for other cancer patients may not be readily generalizable to cervical cancer survivors.

Three questionnaire-based studies investigated return to work in relation to cancer treatment [352-354]. In the study by de Boer et al. [352], return to work was measured at 2, 12 and 18 months after treatment of different cancers with curative intent. In the whole cohort, patients treated with additional chemotherapy and radiotherapy had a 2.4 times higher risk of staying off work compared to patients treated with surgery alone. Also in the study by Amir et al. [353], treatment modality was a significant factor that predicted return to work within 18 months. The highest proportion of returnees was found among those who received surgery alone (93%) and the lowest (71%) in those treated with radiotherapy, chemotherapy or hormone therapy. In the study by Molina et al.

[354], 59% of the cancer patients returned to work within 6 months after diagnosis. The strongest predictors for remaining in employment were young age, complete response and lack of sequelae of the disease and its treatment.

Spelten et al. [355] examined the impact of fatigue in return to work among 235 cancer patients, of which 56 were diagnosed with female genital cancer. Fatigue levels six months after the start of sick leave predicted return to work at 18 months, independent of diagnosis and treatment.

Sick leave and return to work among gynecological cancer survivors

Evaluations of work loss specifically among cervical cancer patients are rare. Two register-based studies have presented results for cervical or gynecological cancer patients [342, 356]. Roelen et al. [356], investigated return to work in 5074 employees, of which 855 were diagnosed with gynecological cancer. Median duration of sickness absence in this subgroup was 105 days during the first 2 years following diagnosis, and 88% had full return to work within 2 years. In the study by Torp et al. [342], 96 (8%) of the 2008 individuals included in 1999 and alive in 2004, at end of follow-up, were cervical cancer patients. Odds ratio for sick leave 5 years after diagnosis, adjusted for socio-demographic factors and sick leave before diagnosis was non-significantly increased for the subgroup of cervical cancer patients (1.34, 95% CI 0.85-2.12) compared to a cancer free comparison group.

A variety of factors influence the decision whether or not to return to work. In a study by Nachreiner et al. [357], gynecological cancer survivors reported challenges in work performance including physical tasks such as lifting, stooping, crouching or kneeling, but also concerns about the effect on concentration, analyzing data and learning new things.

Several studies [358-360], including a meta-analysis [346], have reported higher unemployment rates among gynecological cancer survivors compared to the general population (49% vs 38%; pooled relative risk (RR), 1.3, 95% CI 1.2-1.4). The effect of co-morbidity on unemployment was examined by Yoo et al. [360] in a study including 858 cervical cancer survivors in Korea. The percentage of unemployed survivors increased from 51% to 73% after treatment, and two or more co-morbidities (adjusted OR 1.8, 95% CI 1.1-2.9) were associated with unemployment.

Table 7 presents a summary of studies with data on work loss in cervical or gynecological cancer patients. Most patients returned to work after completed treatment [356, 361]. The rate of return to work, and work ability, increased with time from diagnosis [352, 362] and 5 years from diagnosis, sick leave rates were not significantly increased [342]. Compared to the general population, women with a history of gynecological cancer had an increased risk of unemployment [358, 359], especially when other morbidity was present [360], however there was no excess unemployment when adjustment was made for socio-demographic and work-related variables [363]. Women treated with radiotherapy took longer time to return to work [364]. No study assessed the impact of cancer recurrence on sick leave or unemployment.

Table 7. Studies on work loss among cervical and/or female genital cancer survivors.

	Country	N of patients	Study period	Enrollment criteria	Outcome	Result
Spelten [355], 2003	Netherlands	Gynecological cancer n=56	4-6 to 18 months from first day of sick-leave	Age 18-60 years, employed, treatment with curative intent	Time to partial or full RTW	HR 0.55 (0.33-0.92), compared to male urogenital cancer
Taskila-Åbrandt [358], 2005	Finland	Gynecological cancer n= 5105, cervical cancer n=914	1997	Age 15–64 years, alive Dec 1997	Employment status in 1997	Cervix: 52% employed vs 57% of comparators, OR 0.90 (0.83–0.98) Female genital 48% employed vs 52%, OR 0.93 (0.89-0.97)
Short [365], 2005	USA	Uterine cancer n=76	Sep 2000 - May, 2001	Age 25-62, diagnosis Jan 1997-Dec 1999	Cancer-related work disability	OR for work disability: 0.58 (0.18–1.85), OR for quitting work: 0.38 (0.12–1.21) vs 45-year-old male with stage I colorectal cancer
Bradley [366], 2006	USA	Cervical and endometrial cancer n=152	5-20 years from diagnosis	Diagnosis within 5 – 20 years, no prior or subsequent second cancer	QoL and mental health	Disabled patients had poorer QoL than working patients, adjusted for age, marital status, education
De Boer [352], 2008	Netherlands	Gynecological cancer n=43	6-18 months from first day of sick-leave	Age 18-58 years, employed, treatment with curative intent	Workability score (0-10, where 10=best work ever) at 6, 12 and 18 months	6 months: 3.9±3.1, 12 months 6.3±2.9, 18 months 7.0±2.6
Korfage [359], 2009	Netherlands	Cervical cancer n=291	2-10 years from diagnosis	Diagnosis 1995–2003, alive Jan 2006	Employment rate	41% were employed vs 58% of comparators
Roelen [356], 2011	Netherlands	Gynecological cancer n=855	0-2 years from diagnosis	Age 18-60 years, sickness absence due to cancer, employed at diagnosis	Time to full RTW	Median (range) sickness absence 105 (97-113) days, 88% full return to work 2 years after diagnosis
Roelen [361], 2011	Netherlands	Gynecological cancer n=878	0-2 years from diagnosis	Sickness absence due to cancer Jan 2004 - Dec 2006, employed at diagnosis	Time to partial of full RTW (≥50% of previous earnings for 28 consecutive days)	Median days to partial RTW: 79 (68–90), full RTW: 104 (90–118)
Nachreiner [362], 2012	USA	Gynecological cancer N=110, cervical cancer n=10,	1-21 months from diagnosis	Age ≥21, working at time of diagnosis	Work patterns during the first 6 months	Gynecological cancer: 41% stopped working during month 1, at 6 months 67% worked

Table 7 continued

	Country	N of patients	Study period	Enrolment criteria	Outcome	Result
Torp [342], 2012	Norway	Cervical cancer n=96	5 years from diagnosis	Age 18-61 years, cancer diagnosis 1999, employed Jan 2004, eligible for sickness allowance	Any sick-leave in 2004	OR for sick-leave: 1.34 (0.85-2.12) versus cancer-free comparators, adjusted for socio-demographic factors, previous sick-leave
Torp [363], 2013	Norway	Cervical cancer n=143	5 years from diagnosis	Age 18-61, cancer diagnosis in 1999	Employment in 2004	OR for employment 0.79 (0.51–1.22) versus cancer-free comparators, adjusted for socio-demographic and work-related variables
Cooper [364], 2013	United kingdom	Gynecological cancer n=56	6 and 12 months from diagnosis	Age>18, employed at diagnosis, completed treatment	Time to RTW	Median time to RTW 17.9 (11.0–31.3) weeks. RTW after radiotherapy (n=19): 25.4 weeks, no radiotherapy (n=37): 14.1 weeks
Yoo [360], 2013	Korea	Cervical cancer n=858	1983-2004	Diagnosis and treatment 1983 - 2004, no current cancer or treatment, no other cancer	Unemployment at time of survey	Unemployment at diagnosis: 50.6%, at survey: 72.8%.

RTW, return to work; QoL, quality of life; HIR, hazard ratio; OD, odds ratio

SUMMARY OF AIMS AND RATIONALE

The overall aim of the thesis is to generate knowledge of short- and long term consequences of cervical cancer treatment, to provide a basis for improvement of the quality of life of cervical cancer survivors. Knowledge of factors associated with post treatment morbidity may also benefit patients with other cancers treated similarly, such as the endometrial, ovarian, vulvar, vaginal, bladder, anal and rectal cancer.

The specific research questions were:

I: How are serum levels of AMH affected by cervical cancer treatments?

Rationale: Previous studies have indicated an increased risk of early menopause after hysterectomy [172-177]. Because early menopause is associated with increased morbidity and mortality [251-266] and HT reduces these risks [262, 263, 266], it is important to ensure adequate hormone substitution in such cases [82]. Hysterectomised women have no menses, and therefore the onset of menopause may go unnoticed. AMH is already being used as a marker of iatrogenic damage to the ovarian follicle reserve, due to radiotherapy [185, 186], chemotherapy [185, 367], uterine artery embolization [196], simple hysterectomy [189-195], or ovarian surgery [368, 369]. However, measurements of AMH before and after radical hysterectomy have not been performed previously. A decline in AMH that is larger than the expected decline due to normal ageing could indicate a risk early ovarian failure.

II: How are serum levels of androgens affected by cervical cancer treatments and is there an association between low testosterone levels and low sexual function in this patient group?

Rationale: Sexual dysfunction is common among cervical cancer survivors [216], and the causes are likely multifactorial. It is not known if androgen deficiency contributes to sexual dysfunction among cancer survivors, since the impact of radiotherapy on ovarian androgen production is largely unknown [197-199]. If low androgen levels could be demonstrated among women treated for cervical cancer and if low levels would be associated with sexual dysfunction, the logical consequence would be to offer these women the possibility of testosterone treatment, which has proven effective in the treatment of hypoactive sexual desire and arousal disorders among naturally postmenopausal women [243, 246].

III: To what extent do women in early menopause due to cervical cancer treatment use HT?

Rationale: HT is recommended to women in early menopause up to the age of natural menopause [80-82] for menopausal symptoms and to reduce risks of cardiovascular disease and osteoporosis [279]. HT use has diminished after reports of risks associated with long-term use [271]. The general fear of HT could have led to an underuse also among women in early menopause, however, no study on patient and doctor adherence to the recommendations on HT use among cervical cancer survivors has been performed previously.

IV: Do cervical cancer survivors have an increased risk of work loss?

Rationale: The extent of sick leave and disability pension after a cancer diagnosis can be expected to vary greatly between cancer forms, due to the variations in age at diagnosis, prognosis and treatment [370]. Previous studies in this area including cervical or gynecological cancer patients had limited clinical data and could therefore not distinguish between sick leave due to cancer relapse and sick leave among cured patients [342, 352, 353, 356, 371]. In the absence of relapse, an increased risk of sick leave and disability pension may be viewed as a proxy for severe side effects of treatment, which potentially could be prevented or treated.

PATIENTS AND METHODS

Table 8. Overview of the four studies in the thesis.

	STUDY I	STUDY II	STUDY III	STUDY IV
Type of study	Clinical cohort study	Register-based cohort study	Register-based cohort study	Register-based cohort study
N of patients	32 (of whom 29 were participants in study II)	60	837	1971
N of comparators	-	-	-	9254
Ages (years)	23-44	23-85	20-45	18-60 years
Study period	<i>Inclusion:</i> Sep 1 st 2008-Aug 31 st 2009 <i>Follow-up:</i> Aug 31 st 2010	<i>Inclusion:</i> Jan 1 st 2005 - Sep 30 th 2009 <i>Follow-up:</i> Apr 1 st 2011	<i>Inclusion:</i> Jan 1 st 2003 to Dec 31 th 2009 <i>Follow-up:</i> Sep 30 th 2013	<i>Inclusion:</i> Jan 1 st 2003 to Dec 31 th 2009 <i>Follow-up:</i> Sep 30 th 2013
Data sources	Study protocol Patient charts	Study protocol Patient charts	Cancer register, NPR, TPR, Prescribed Drug register	Cancer register, NPR, TPR, SSIA, MIDAS, LISA
Exposure	Treatment to ovaries: radiotherapy, oophorectomy, ovarian-sparing surgery	Cervical cancer treatment (oophorectomy or radiotherapy)	Cervical cancer treatment	Cervical cancer treatments
Outcome measures	<i>Hormones:</i> AMH, FSH, estradiol <i>Hormones:</i> testosterone, SHBG, androstendione, DHEAS, FSH, LH, estradiol <i>Questionnaires:</i> FSFI, PGWB, study-specific questionnaire	<i>Hormones:</i> testosterone, SHBG, androstendione, DHEAS, FSH, LH, estradiol <i>Questionnaires:</i> FSFI, PGWB, study-specific questionnaire	HT use and doses of HT (DDD)	Mean annual days on sick leave and disability pension, occurrence of disability pension during follow-up.
Statistical analyses	Wilcoxon signed rank test	Wilcoxon signed rank test, Mann Whitney U test, Kruskal-Wallis test, Mc Nemar's test, Fisher's exact test, Spearman's rank correlation coefficient	Jonckheere-Terpstra test, Chi-square test	Linear regression, Cox regression

AMH, Anti-Müllerian hormone; FSH, Follicle-stimulating hormone; SHBG, Sex-hormone binding globuline; DHEAS, dehydroepiandrosteredione sulphate; FSFI, Female sexual function index; PGWB, Psychological general wellbeing index; NPR, National patient register; TPR, Total population register; HT, hormone therapy; DDD, designated daily dose; SSIA, The Swedish Social Insurance Agency; MIDAS, MikroData för Analys av Socialförsäkringen; LISA, Longitudinal integration database for health insurance and labour market studies

STUDY I-II: CLINICAL STUDIES

Investigations I and II are based on a pilot study, including data collected from a one-year cohort of cervical cancer patients at Radiumhemmet, Karolinska University Hospital from September 1st 2008 to August 31st 2009.

Population

The aim was to include all women eligible for cervical cancer treatment. Exclusion criteria were:

1. Inability to communicate in Swedish (because we used questionnaires in Swedish).
2. WHO performance status [372] two or higher (no curative treatment possible).

At their first visit, before clinical staging and treatment, the women were asked to participate in the study. A total of 92 patients were asked to participate, of whom 71 consented (77%). From these women, a subgroup was chosen for analysis of AMH levels (Figure 6), consisting of women < 45 years of age, treated with chemoradiotherapy or radical hysterectomy. The women treated with trachelectomy (n = 3) were not analyzed further due to the small number. The study population in study I thus consisted of 32 women.

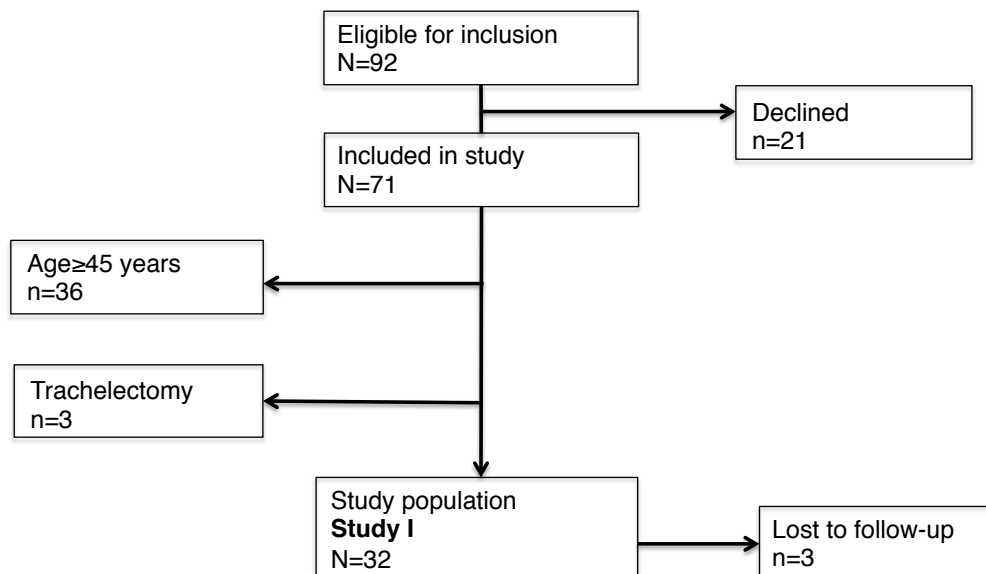


Figure 6. Flow-chart of the participants in Study I.

From the 71 women originally included in the study, 11 were lost to follow-up, mainly due to cancer progression. In study II, we selected all women with complete before and after treatment blood sampling (n = 60).

Exposure

Data on tumor stage (according to FIGO) and treatment(s) were obtained from the women's medical charts. The participants were then divided into groups according to how their individual treatment(s) affected ovarian sex hormone production. The groups in study I were defined as:

Treatment group 1: Chemoradiotherapy only, no surgery (n = 17).

Treatment group 2: Hysterectomy, pelvic lymphadenectomy and SOE with or without preoperative brachytherapy with or without postoperative chemoradiotherapy (n = 6).

Treatment group 3: Radical hysterectomy and pelvic lymphadenectomy with ovarian preservation (n = 9).

The treatment groups in study II were defined as:

Irradiated ovaries: Radiotherapy (with or without chemotherapy) without surgery or ovarian-sparing surgery and postoperative radiotherapy (with or without chemotherapy) (n = 38)

Removed ovaries: Radical hysterectomy, pelvic lymphadenectomy and SOE with or without radiotherapy or chemotherapy (n = 10)

Preserved ovaries: Ovarian-sparing radical hysterectomy or trachelectomy and pelvic lymphadenectomy (n = 12).

Outcome

Blood-sampling and measurement

Blood samples were taken at baseline, 1-2 weeks after brachytherapy or radiotherapy, and one year after the last treatment (but results will only be presented for the baseline and 1-year blood samples). For practical reasons, the blood sampling had to be performed opportunistically regarding time of day and menstrual cycle day. Blood samples were allowed to clot for 30-60 minutes, and after centrifugation for 10 minutes in 3000g, the serum was placed in a freezer at -20°. The analyses were performed in batch.

Details of the different hormone assays are described in Table 9. Serum AMH was determined by enzyme linked immunoabsorbent assay AMH Gen II ELISA by Beckman Coulter. Detection limit reported by the manufacturer was 0.08 $\mu\text{g/L}$, within and between assay coefficient of variation 5.4% and 5.6%, respectively. The normal reference range of serum AMH by this method at the Department of Clinical Chemistry, Karolinska University Hospital is 0.7-6 $\mu\text{g/L}$.

Serum levels of FSH, LH, SHBG, androstenedione and DHEAS were determined by direct chemiluminescent immunometric assay (Immulite, Siemens) and levels of estradiol were determined by radioimmunoassay (Spectria, Orion Diagnostica).

Total testosterone was determined by liquid chromatography-tandem mass spectrometry (MS Quattro Premier, Xevo TQ MS). Detection limit was 0.1 nmol/L and within and between assay coefficient of variation 2.7 (7%) and 13 (6%), respectively. Concentrations of free testosterone were determined by calculations including testosterone, SHBG and a fixed concentration of albumin (40 g/L)[373] using the Södergård equation [374].

Table 9. Overview of assays used in studies I and II.

Hormone	Assay name	Manufacturer	Method	Reference value reported by the manufacturer	Intraassay precision (CV)	Interassay precision (CV)
AMH	AMH Gen II Elisa	Beckman Coulter	Enzyme linked immunosorbent assay (ELISA)	ND-12.6 µg/L	3.4-5.4%	4.0-5.6%
FSH	Immulite 1000 FSH	Siemens	Chemiluminescent immunometric assay (ChLIA or CLIA)	Premenopausal: 1.2-21 IU/L Postmenopausal: 21.7-153 IU/L	2.6-3.7%	5.8-6.7%
LH	Immulite 1000 LH	Siemens	Chemiluminescent immunometric assay (ChLIA or CLIA)	Premenopausal: ND-77 IU/L Postmenopausal: 11.3-39.8 IU/L	4.8-6.5%	7.2-26%
SHBG	Immulite 1000 SHBG	Siemens	Chemiluminescent immunometric assay (ChLIA or CLIA)	18-114 nmol/L	4.1-7.7%	5.8-13%
A	Immulite 1000 Androstenedione	Siemens	Chemiluminescent immunometric assay (ChLIA or CLIA)	1-12.2 nmol/L	5.1-9.1%	6.4-15.2%
DHEAS	Immulite 1000 DHEA-SO ₄	Siemens	Chemiluminescent enzyme immunoassay (CLEIA)	35-430 µg/dL	6.8-9.5%	8.1-15%
Estradiol	Spectria Estradiol Sensitive RIA	Orion Diagnostica	Radioimmunoassay (RIA)	Premenopausal: 105-1399 pmol/L Postmenopausal: 11-50 pmol/L	2.8-18.1%	5.8-17.6%

AMH, Anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globuline; A, androstenedione; DHEAS, dehydroepiandrosteredione; ND, not detectable; CV, coefficient of variation

Quality of life assessment

Aspects of quality of life were assessed at baseline and at one-year follow-up. At baseline (date of inclusion, before start of treatment), the women were asked to assess their scores before the start of cancer symptoms. At one-year follow-up, (i.e. one year after end of treatment) they were asked to answer the questionnaires concerning mood and symptoms during the past four weeks. The women completed three questionnaires, but here, results will only be presented from the FSFI questionnaire. The questionnaires were completed in conjunction with a hospital visit.

The female sexual function index (FSFI) is an assessment tool for female sexual dysfunction [375]. The 19-item survey assesses 6 domains of sexual function: desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items) and discomfort/pain (3 items). The responses are graded on a scale from 0 or 1 to 5. A scoring algorithm is generated to assess each domain. Domain scores are obtained by summing the scores of the questions in each domain, and then multiplying the sum by the domain factor. The total score, which ranges from 2 to 36, is obtained by summing the six domain scores. A higher score means better sexual function. The clinical cut-off indicating sexual dysfunction is 26.5 [376], but for a diagnosis of female sexual dysfunction it needs to be combined with a measurement of distress [377]. The Swedish version of the FSFI was examined in a population of women with and without a diagnosis of HSDD and showed good reliability (Cronbach's alpha: 0.90-0.96, test-retest $r=0.86-0.93$), and correlation between the FSFI and the sexual function questionnaire (SFQ) ($r=0.74-0.87$) [317]. The FSFI is recommended as a measure of symptom severity for heterosexual women, who have been sexually active in the past 4 weeks [377].

Follow-up

The women were followed from date of inclusion up to one year after treatment, at the latest August 31st 2010.

Ethical permission

The study was approved by the Regional Research Ethics Committee in Stockholm (Dnr 03-645). Written informed consent was obtained from all women.

Statistical analyses

To compare differences between groups, parametric tests can be used if the data is normally distributed. However, the *Shapiro-Wilks test* [378] showed that much of the data was not normally distributed. Therefore, the following non-parametric tests were used:

The Wilcoxon signed-rank test [379] was used to compare hormone levels from before to after treatments in studies I and II and FSFI scores from before to after treatments in study II.

The Mann–Whitney U test [380] (also called the Wilcoxon rank-sum test) was used to compare androgen levels between pre- and postmenopausal women, and to compare age and hormone levels between women with FSFI < 26.5 and women with FSFI \geq 26.5 at one-year follow-up.

The Kruskal–Wallis test [381] was used to compare differences in hormone levels and FSFI scores between the three treatment groups.

McNemar’s test [382] was used to compare the proportions of women with low sexual function (FSFI < 26.5) from before to after treatment.

Fisher’s exact test [383] was used to compare the proportions of women with low sexual function before and after treatment in the three groups, and to compare factors that may affect sexual function among women with FSFI < 26.5 and women with FSFI \geq 26.5 at one-year follow-up.

Spearman’s rank correlation coefficient [384] was used to investigate correlations between androgen levels and FSFI scores.

All statistical tests were two-sided and $p < 0.05$ was considered significant. Statistical analyses were performed using IBM SPSS Statistics version 20 and 22.

STUDY III-IV: REGISTER STUDIES

Studies III and IV are register-based studies, where record linkage between the different registers was possible through the personal identification number assigned to all Swedish residents [385].

Registers used

The Swedish Cancer Register [386] was founded in 1958 and is maintained by the National Board of Health and Welfare (NBHW). It is estimated to cover 96% of all cancer cases in the population [387]. The register contains data on tumor site and histology according to the International Classification of Diseases (ICD) [388], date of diagnosis and reporting hospital. Tumor stage according to FIGO is also included from the year 2003 and onwards with gradually increasing coverage.

The Swedish National Patient Register (NPR) [389] is maintained by the NBHW. The NPR was established in 1964-65 and has covered the entire Swedish population since 1987. It provides dates of hospital admissions in Sweden and discharge diagnoses coded according to ICD. Until 1996 up to 6 discharge diagnoses and operation codes were permitted and a national classification of procedures was used based on an American classification of surgical procedures. After 1996 up to 8 discharge diagnoses were permitted and up to 12 operation codes from the Swedish Classification of Operations and Major Procedures. The ICD-9-classification was used 1987-1996 and the ICD-10 from 1997. From 1997, day-surgery was also included in the register and from 2001 specialized outpatient visits. The validity of the NPR is regarded as high [390].

The Prescribed Drug Register [391], maintained by the NBHW, was established on July 1st 2005 and holds data on dispensed prescriptions (not prescriptions actually issued by physicians) to the whole population of Sweden, including dispensed item (substance and formulation), amount, date of dispensing, and the prescriber's profession and practice. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) Classification System [392]. The register does not include data on over the counter medications and drugs used in hospitals.

The Total Population Register [393] started in 1968 and is maintained by Statistics Sweden (SCB). It records dates of emigration and death of all residents in Sweden, and is continuously updated.

The Longitudinal integration database for health insurance and labour market studies (LISA) [394] is maintained by SCB since 1990 and includes all individuals from 16 years of age that were registered in Sweden as of December 31 each year. The database integrates data from the labor market, educational, and social sectors and is updated each year.

The MikroData för Analys av Socialförsäkringen (MIDAS) [395] is maintained by the Swedish Social Insurance Agency (Försäkringskassan). It holds information on compensation for sickness, rehabilitation, work injury, and permanent disability. Only sick leave episodes >14 days are recorded, since the first two weeks of sick leave are paid by the employer. Disability pension is recorded from the first day.

Populations

Women with first incident cervical cancer were identified through the Swedish Cancer Register.

In study III (Figure 7), we selected women 45 years or younger at diagnosis. To ensure a minimum follow-up time of 1.5 years after diagnosis, women who died or emigrated within this time period were excluded. Also, women with previous breast cancer were excluded, since it is usually a contraindication for HT. The prescribed drug register has information on dispensing from July 1st 2005 and therefore the time period January 1st 2005 to Sep 30th 2009 was chosen, to ensure that information on dispensing from 0.5 to 1.5 years after diagnosis was available for all patients at the time of our investigation in 2011.

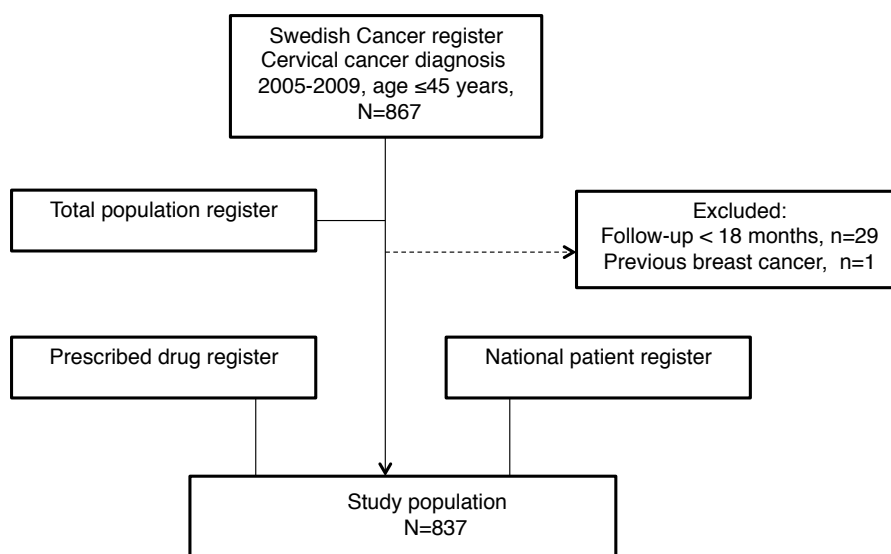


Figure 7. Flow-chart of participants and registers used in Study III.

In Study IV (Figure 8), we selected women aged 18-60 years at cervical cancer diagnosis during the period January 1st 2003 to December 31st 2009. Randomly selected general population comparators were individually matched to the cervical cancer patients by age, calendar year, region of residence and highest attained education level before diagnosis/match date. The comparators were not allowed to have a history of cervical cancer at the time of diagnosis of the matched case, and were censored in case of cervical cancer during follow-up. 1718 patients (87%) were matched to five comparators each, 78 patients (4%) were matched to four, 52 patients (3%) were matched to three, 73 patients (4%) were matched to two, and 50 patients (3%) were matched to one comparator each.

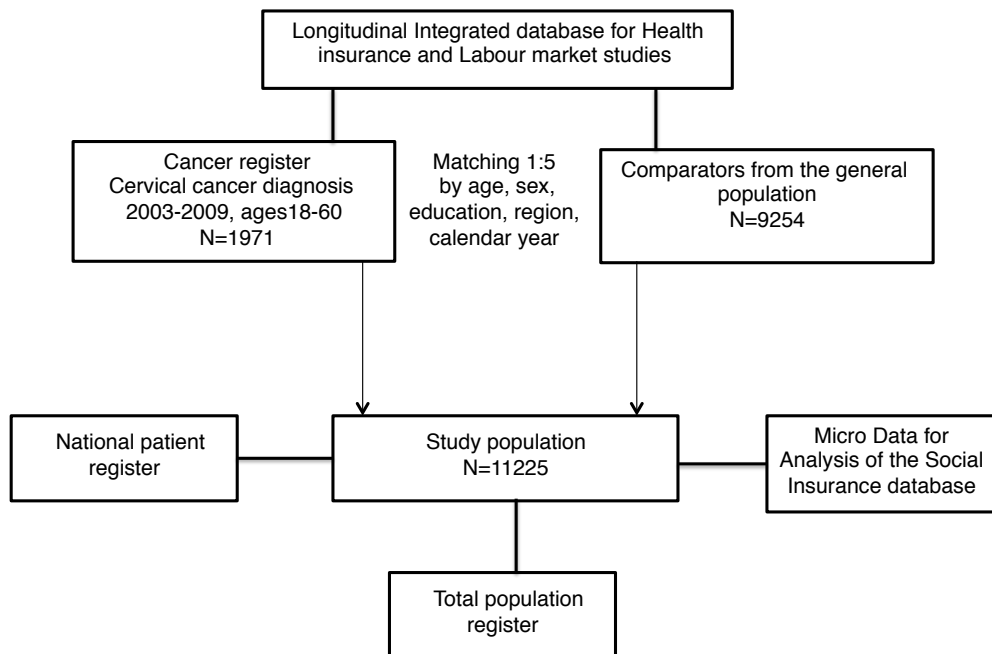


Figure 8. Flow-chart of participants and registers used in study IV.

Exposure

The exposure was cancer treatment. Codes for surgical and oncological procedures from 6 months before, up to one year after the cervical cancer diagnosis, were taken from the NPR and defined the cancer treatment of each individual (Appendix).

In study III, the women were divided into 3 groups based on cervical cancer treatment regimen:

- Those expected to have estrogen deprivation due to bilateral SOE or radiotherapy were categorized as “in need of HT”.
- Women treated surgically without SOE or radiotherapy (ovarian-sparing surgery) were categorized as “not in need of HT”.
- Women who had unilateral SOE or received chemotherapy without radiotherapy were categorized as “in potential need of HT”, since unilateral SOE may be associated with early menopause [396] and some chemotherapeutic agents affect ovarian function [397].

Women with a previous history of uni- or bilateral SOE (at any time point between 1987 and the uterine cervical cancer diagnosis) were classified according to their final treatment status (hysterectomy and unilateral SOE or hysterectomy and bilateral SOE).

In Study IV the women were divided into 4 major treatment groups, and these treatment groups may be seen as proxy variables for cancer stage:

- Fertility-sparing treatment (conization or trachelectomy) (very early stages)
- Hysterectomy alone, no radiotherapy or chemotherapy (early stages)
- Hysterectomy plus chemo- and/or radiotherapy (early stages with adverse prognostic factors)
- Chemo- and/or radiotherapy, no surgery (advanced stages)

In study IV cancer relapse was defined at the first registration in the NPR of an ICD-code for a secondary malignant tumor (Appendix), i.e. metastasis, at the earliest 6 months before cervical cancer diagnosis. If a woman received radiotherapy or chemotherapy in combination with a diagnosis of cervical cancer more than one year after primary cervical cancer diagnosis she was also classified as having a relapse.

Outcome

In study III, information on dispensing of contraceptives (G03A), estrogens (G03C), progestogens (G03D) and progestogens and estrogens in combination (G03F) were obtained from the Prescribed Drug Register. The drugs were further classified in subgroups of HT according to type of hormone and formulation as follows: patch/gel/oral estrogens with or without progestogens, contraceptives, or vaginal estrogen.

HT dispensing was summarized in half-year intervals starting from the date of diagnosis to end of follow-up. Women were defined as prevalent users of HT in a specific interval if they had at least one dispensing during that time, among all women who were alive and not emigrated by the end of the time period in question. Assessment of daily dose of HT was based on recommended dose, or designated daily dose (DDD), equaling 182 for a half-year period, i.e. one dose per day during half a year. The DDD's for transdermal preparations are estimated based on the amount of active ingredient delivered per 24 hours and the number of days each patch is used. The dose used during each half-year period was estimated based on the dose and frequency of dispensing as the percentage of the recommended dose dispensed during each half-year period: one daily dose for ≥ 135 out of 182 days ($\geq 75\%$), one daily dose for 90 to 134 out of 182 days (50-75%), one daily dose for 45 to 89 days out of 182 days (25-50%), one daily dose for less than 45 out of 182 days ($< 25\%$).

We focused on HT use during the period 0.5-1 year after diagnosis, but also assessed use during a full one-year period 0.5-1.5 years after diagnosis to allow for carry-over effects of dispensing between periods. In addition, we assessed use during the entire follow-up period in women considered in need of HT.

In study IV the exact dates of sick leave and disability pension were retrieved from the Social Insurance database [398]. The net number of lost workdays of sick leave or disability pension per year of follow-up was calculated by multiplying the number of days with the proportion of compensation received [399]. The occurrence of disability pension was also assessed separately during follow-up.

Co-variates

In study III, age, FIGO stage, year of diagnosis, and histopathology were taken from the Cancer Register.

In study IV data on education level, unemployment occurring in the time period 1-2 years before diagnosis and family situation at diagnosis or match year was taken from the LISA database. From the Social Insurance database MIDAS we retrieved information on sick leave occurring in the time period 1-2 years before diagnosis (the year prior to diagnosis was not considered due to potential association with early cancer symptoms).

Follow-up

In study III the women were followed from cervical cancer diagnosis up to maximum 50 years of age (menopausal age), migration, death, or end of the study period (April 1st 2011), whichever came first.

In study IV patients and comparators were followed from date of diagnosis or match date up to maximum 65 years of age (retirement), migration, death, or end of the study period (September 30th 2013), whichever came first. In the analysis of relapse-free patients versus comparators, date of cancer relapse (as recorded in the NPR) was additionally included as an end of follow-up, and patients and participants were censored 3 months before end of follow-up. The three-month lag period was used in this analysis to avoid influence of sick leave and disability pension related to early symptoms of cancer relapse.

Ethical permission

The regional ethics board in Stockholm approved both studies (Dnr 2007/1335-31/4 and 2010/1624-32).

Statistical analyses

In study III, the *Jonckheere-Terpstra test* [400, 401] was used to compare doses of HT for variables with an assumed a priori ordering, i.e. FIGO stage (0,I, II, III-IV) year of diagnosis (2005, 2006, 2007, 2008, 2009) and age (22-29, 30-34, 35-39, 40-45). The Jonckheere-Terpstra test is similar to the Kruskal–Wallis test in that both tests rely only on the ordering of the outcome, however, when there is an *a priori* ordering also of a predictor, the Jonckheere-Terpstra test has more statistical power than the Kruskal–Wallis test which assumes unordered groups in the predictor. The *Pearson Chi-squared test* [402] was used to examine if doses of HT differed between patient groups with different tumor histopathology (adenocarcinoma, squamous cell carcinoma, other).

In study IV, the mean number of lost workdays per year during follow-up after diagnosis or match date was assessed among patients and comparators, and differences were computed using multivariable linear regression, adjusted for age (<30, 30-39, 40-49, 50-60 years), match year (2003, 2004, 2005, 2006, 2007, 2008, 2009), region (North, Uppsala-Örebro, Stockholm, South-East, West, South), education (0-9, 10-12, >12 years), family situation at diagnosis/match year (single with children, single without children, couples with children, couples without children) and for sick leave (yes/no), disability pension (yes/no) and unemployment (yes/no) 1-2 years before diagnosis or match year. The variables for adjustment were chosen *a priori*, based on previous knowledge of possible confounding factors [342, 403-407].

Linear regression assumes - apart from linearity of the relationship between dependent and independent variables - statistical independence of the errors, constant variance of the errors and normality of the error distribution, which cannot be assumed if the population is unknown. *Bootstrapping* (coined by Efron in 1979) [408], allows estimation of the empirical sampling distribution of the data. The basic idea of bootstrapping is to draw inferences about a population by *resampling* the sample data and performing inference on the resample. In bootstrap-resamples, the “population” is in fact the sample, and this is known; hence the quality of inference from resample data to the “true” sample is measurable. Confidence intervals were estimated by taking the 5th and 95th empirical percentiles from the bootstrap distribution of the estimated parameter.

Cox regression [409], or Cox proportional hazards regression, is a method for investigating the effect of several variables upon the time a specified event takes to happen. The Cox model estimates the *hazard ratio* (HR), i.e. the relative event rate when comparing two groups over the study follow-up. The HR of disability pension was calculated using the Cox regression model and patients with disability pension before diagnosis were excluded in those analyses. An important assumption is that the effects of the predictor variables are constant over the study follow-up. To test if predictor variables are constant over time, several methods are available. We used the Grambsch-Therneau test of trend in Schoenfeld residuals [410] and found no evidence that the proportional hazards assumption was violated. In multivariable analyses of risk of disability pension, the Cox model was adjusted for the matching variables (age, calendar year, region, education) and for family situation and previous unemployment and previous sick leave. Associations of socio-demographic factors with risk of disability pension during follow-up among the cervical cancer patients were examined by Cox regression with adjustment for the same variables. The interaction between sick leave and cancer treatment (effect modification) was examined by the likelihood-ratio test.

All statistical tests were 2-sided and $p < 0.05$ was considered significant. SAS (version 9.2 and 9.4, SAS Institute Inc, Cary, NC, USA) and STATA (StataCorp, release 12 and 13, College Station, TX, USA) software were used.

RESULTS OF STUDY I-IV

STUDY I: AMH after cervical cancer treatments

After radical hysterectomy, pelvic lymphadenectomy and SOE (n = 6) or chemoradiotherapy (n = 14), serum levels of AMH were undetectable in all women, and 16 of 20 women were on HT. After radical hysterectomy and pelvic lymphadenectomy with ovarian preservation (n = 9), mean serum AMH decreased by 0.9 ± 0.7 µg/L, from 2.0 ± 1.4 , representing a 45% reduction. Serum levels of FSH changed from 5.5 ± 1.6 to 5.9 ± 2.9 IU/L and estradiol from 204 ± 93 to 228 ± 169 pmol/L (not significant). All women with preserved ovaries had serum FSH values < 30 IU/L one year after surgery.

STUDY II: Testosterone and sexual function after treatment

Among women with irradiated ovaries (n = 38), serum levels of FSH and LH increased from baseline to one year after radiotherapy with or without chemotherapy in both pre- and postmenopausal women and estradiol decreased. Simultaneously, the median serum level of total testosterone decreased from 0.6 to 0.4 (-29%) in premenopausal women (n=16) and from 0.7 to 0.5 (-25%) in postmenopausal women (n = 22). Serum levels of free testosterone decreased from median 9 to 6 pmol/L (-22%) in premenopausal women and from median 8 to 6 pmol/L (-29%) in postmenopausal women. For androstenedione, premenopausal, but not postmenopausal, women had a median value that was lower one year after radiotherapy, whereas median DHEAS was lower at one-year follow-up only among the postmenopausal women.

As expected, serum FSH increased among premenopausal women with removed ovaries (n = 10) but not among those with preserved ovaries (n = 12). In contrast to premenopausal women with irradiated ovaries, serum levels of total and free testosterone and androstenedione were not significantly reduced among premenopausal women with removed ovaries.

Before treatment, 83% of the women in the irradiated ovaries group and 90% of women in the removed ovaries group had FSFI < 26.5, suggestive of sexual dysfunction, versus 36% of the women in the preserved ovaries group. Median total FSFI-score differed by treatment at baseline and the lowest scores were found among women in the irradiated ovaries group. At one-year follow-up, total FSFI scores no longer differed by treatment. All groups had a tendency towards higher scores at one-year follow-up compared to baseline values, although not statistically significantly higher. At one-year follow-up, the proportion of women with FSFI < 26.5 was 80% for patients with irradiated ovaries, 44% for those with removed ovaries and 40% for those with preserved ovaries. Correlations between total and free testosterone, androstenedione and

FSFI scores at one year were examined among women with complete FSFI-questionnaires who had reported being sexually active at baseline (n=39), by treatment group. No pattern of correlation was seen.

We compared characteristics of women with FSFI < 26.5 (n=24) to those with FSFI \geq 26.5 (n=15) one year after treatment. The two groups did not differ regarding age, partnership status, and sexual function at baseline or use of HT or vaginal estrogen. Women with FSFI \geq 26.5 had lower FSH levels, while other hormones, including all androgens, were similar.

STUDY III: HT use after radiotherapy or surgical castration

Among all women classified as “in need of HT”, based on recorded treatment (n=257), 46% had dispensing corresponding to 75% or more of recommended dose (1 tablet/day for at least 135 of 182 days) during the period 0.5 to 1 year after diagnosis. HT doses differed by age: 64% among women aged 22-29 years versus 33% among women aged 40-45 years dispensed at least 75% of full dose. There were no differences in HT doses used by calendar year of diagnosis, FIGO stage, or histopathology.

Over the entire follow-up period, the proportion of HT users diminished gradually. During the period 4.5 to 5 years after diagnosis 39% of the women considered in need of HT and available for follow-up during that period had at least one dispensing, and 21% dispensed \geq 75% of the recommended dose. Among women aged 22 to 39 years at diagnosis, 79% were HT users 0.5 to 1 year after diagnosis and 56% dispensed \geq 75% of recommended dose, decreasing to 45% for any use at 4.5 to 5 years, and 21% for \geq 75% of recommended dose. Among women aged 40 to 45 years, 32% were users at the end of follow-up and 21% dispensed \geq 75% of recommended dose (compared with 50% and 33%, respectively at 0.5 to 1 year).

When HT use was examined for the time period 0.5-1.5 years from diagnosis (365 days instead of 182 days) the proportion of users increased from 67 to 71% but the proportion of women dispensing \geq 75% of recommended dose was unchanged at 46%.

STUDY IV: Work loss among cervical cancer survivors

During the first year following diagnosis, 75% of the cervical cancer patients (n = 1971) experienced sick leave or disability pension the whole (365 days) or part (< 365 days) of the year, and this was true for 39% during the second year, and 32% the third year. Among the comparators (n = 9254) 13-25% had part- or full time sick leave or disability pension during follow-up. Overall, cervical cancer patients had more lost workdays than comparators up to 8 years following diagnosis (first year: mean difference 71 days [95% CI 66-76]; 8th year: mean difference 9 days [95% CI 2-16]). When disregarding time after relapse, as classified based on relapse and re-treatment codes, relapse-free cancer survivors had a higher mean number of lost workdays versus comparators up to 4 years following diagnosis (mean difference 4th year: 6 days [95% CI 1-11], p<0.05).

Mean number of lost workdays during follow-up differed between treatment groups, which was partly explained by age differences. Women treated with fertility-sparing surgery (median age 33 at diagnosis) had more lost workdays than their comparators only during the first year following diagnosis, with similar results for relapse-free patients versus comparators. Women treated with hysterectomy alone (median age 42 years) had more lost workdays than their comparators up to 8 years following diagnosis, and this was true up to 3 years among the relapse-free versus comparators. Women treated with surgery plus chemo- and/or radiotherapy (median age 42 years) had more lost workdays versus their comparators up to 5 years and the relapse-free up to 3 years. Women with chemo- and/or radiotherapy as only treatment (median age 50 years) had more lost workdays for 5 years overall, and for 4 years among the relapse-free.

The adjusted HR (aHR) of disability pension during follow-up was 2.4-fold increased (95% CI 1.8-3.1) among all cervical cancer patients and 1.9-fold increased (95% CI 1.4-2.7) among relapse-free patients versus comparators. Relapse-free women treated with hysterectomy (aHR 1.8 [95% CI 1.1-2.8]), hysterectomy plus chemo- or radiotherapy (aHR 2.5 [95% CI 1.2-5.4]) or chemo- or radiotherapy alone (aHR 3.0 [95%CI 1.3-6.8]) were at increased risk, whereas women treated with fertility-sparing surgery were not.

Among the patients only, treatment type and pre-diagnostic sick leave, but not education, family type or pre-diagnostic unemployment, were associated with risk of disability pension. In particular, women with previous sick leave treated with chemo- or radiotherapy (with or without surgery) had an 8-fold risk of disability pension compared to women without previous sick leave treated with surgery alone. This high risk was present also when only relapse-free patients were considered. When testing the interaction between previous sick leave and treatment using the likelihood-ratio test, it was significant in the whole group of cervical cancer patients, but not among the relapse-free.

LIMITATIONS

The choice of study design is typically a trade-off between validity and efficiency, and clinical studies are expensive and time consuming. Studies I and II are based on a pilot study with limited sample size and statistical power. The register-based studies III and IV have the advantage of larger materials, but lack detailed information, which may have introduced some misclassification, and limited the possibility to control for confounding.

VALIDITY

Most systematic errors can be categorized as selection bias, information bias or confounding. A systematic error is not dependent on study size and can be avoided through a correct study design.

Selection bias

Selection bias occurs when the association between the exposure and the outcome is different between those who participate and those who do not participate in a study. In the clinical cohort that was used in studies I and II, the inclusion rate was quite high, but several patients were lost to follow-up, or did not complete the questionnaires, giving a response rate for total FSFI scores of $48/92 = 52\%$. We have no reason to believe that the women who declined participation or were lost to follow-up had different hormone levels than the women who completed the study, but the questionnaire results may have been biased. It is possible that women who were lost to follow-up differed regarding sexual function to that of those who completed the study. Because only women with complete data could be evaluated, this may have biased our findings regarding the FSFI questionnaires towards better or worse sexual function.

Papers III-IV have a population-based design, which minimizes selection bias. The Swedish Cancer Register has a high overall completeness and for most epidemiological use, the underreporting is thought to be without major impact [387].

Information bias

Information bias can occur if the collected information is incorrect. The exposure and outcome can be misclassified in two principally different ways: differentially or non-differentially.

Differential misclassification

Differential misclassification may arise when the exposure is misclassified unequally in the population, depending on if the individual has the outcome or not (and vice versa).

In study II, the fact that the women took part in the study and were asked about sexuality could in itself have affected the way they responded. The study participation could have made the women more attentive of symptoms indicating sexual dysfunction, and hence, at one-year follow-up they may have reported more distressful symptoms than they would have otherwise. It is also possible that bringing up these issues at an early stage reduced the risk of future sexual problems and thus lowered the incidence of low sexual function at one-year follow-up.

In study IV, disease relapse was based on diagnoses of metastases and re-treatment codes in the NPR and some underestimation of relapse was possible, especially in untreated/very sick patients. However, we believe such misclassification to be rare, due to the relatively young age of the study cohort.

We did not have access to the exact retirement dates in study IV, and instead patients and comparators were followed until age 65 years. A person that is diagnosed with cancer at an age close to retirement may stop working and retire early. However, a retired person cannot get sick leave compensation or disability pension, and therefore early retirement (before 65 years of age) would lead to a reduction in registered work loss days in our cancer population and, if anything, an attenuation of the true risks compared with the population. Hence, this possible bias cannot explain the increased risks of sick leave and disability pension that we observed.

Non-differential misclassification

Non-differential misclassification typically occurs when the measurement error of exposure or outcome is unrelated to the other factor of interest. Such bias arises from misclassification of the exposure or outcome that is similarly distributed in the study population. Such error is usually of minor concern in epidemiological studies, since it does not shift risk estimates, but only dilutes the estimates towards a null result (although there are exceptions to this rule [411]). Positive associations are therefore most often not explained by non-differential misclassification. However, important associations can be concealed by non-differential misclassification, and therefore, depending on the research question, this could also represent a serious limitation.

Within and between assay variation regarding the results of the hormonal analyses in study I-II is a potential source of error. Different assays are not comparable, and therefore all analyses for each hormone were performed in batch. The fact that blood-samples were not taken at a specific time of day and menstrual cycle day could have affected the hormone results [79, 412, 413]. It was not possible to standardize blood sampling for practical reasons. However, generally serum AMH has been reported to have low intra-cycle variation [95]. Serum testosterone, however, has quite large menstrual [413] and diurnal [79] variation, at least in women of fertile age, which thus affected the results from study II, giving a wider distribution of hormone values, and limiting precision.

The evaluation of sexual function in study II was limited to the past 4 weeks at one-year follow-up, thus assessing a point prevalence of sexual function, but for baseline sexual function the women were asked to evaluate function before start of cancer symptoms. The baseline questionnaires could have been affected by bias due to imprecise recollection, or be negatively affected by the recent cancer diagnosis. The FSFI-scores were low at baseline, which indicates that perhaps the women did not answer the questionnaires as instructed, but rather described their current situation. To allow comparison on a fuller data set, missing data from the FSFI questionnaire were imputed using means from the same domain. Imputed data can be inaccurate, but since only one item per domain was allowed to be imputed, it is improbable that this has affected the findings in any major way.

The scoring of the FSFI can be problematic, because 15 of the 19 items of the FSFI give a score of zero for “No sexual activity” or “Did not attempt intercourse.” Thus, the scoring system misclassifies sexually inactive women as having low sexual function [414, 415]. A woman may have a variety of reasons other than low sexual function that explain a 4-week period without sexual activity or intercourse. Only the two questions that make up the desire domain and two of the three questions that make up the satisfaction domain provide answers that are independent of the occurrence of sexual activity. Also, one question cannot be answered if a woman does not have a partner. This problem is usually addressed by restricting study inclusion to women who report sexual activity over the 4-week time period, as we did in our study.

The NPR that was used in study III and IV to classify the cancer treatment of each individual was originally designed to collect data on health care use, but is today also a source for management and financing. Financial incitements may influence diagnostic coding routines, which probably changes epidemiologic patterns over time and also can lead to differences in coding patterns between hospitals [390].

The validity of the NPR with regard to cervical cancer treatments has not been examined, but for other surgical procedures it has a high sensitivity when comparing to national quality registers [416], and high positive predictive values when comparing to medical records, i.e. patient charts [417, 418]. The validity of the register as a whole is regarded high and the validity is thought to be higher in patients with severe disease (such as cancer) as opposed to mild disease [390]. However, in study III, it is possible that some cancer treatments were not recorded in the NPR and that the number of patients receiving castrating treatment was underestimated. However, since the use of HT was lower in all other treatment groups (including those with missing treatment information), it is unlikely that we have underestimated the true prevalence of HT among patients with treatment-induced early menopause based on misclassification of cancer treatment. It is also possible that some women could have contraindications to HT unknown to us. However, it is unlikely that this would apply to all 33% of the women deprived of endogenous estrogen with no dispensing.

In study IV, only sick leave episodes >14 days were recorded in the register, and therefore the mean number of lost workdays is an underestimation of the total burden of sick leave. This, however, also applied to the comparators and should therefore not affect the observed differences. Disability pension, the main reason for long-term work absence, was registered from the first day. It is also possible that cervical cancer patients had more short-term sick leave than the comparators, something we were unable to discover, since these short-term sick leave episodes were not recorded in the database.

Confounding

Confounding is of central importance in any epidemiologic study; it refers to the mixing of effects. The definition of a confounding factor states that it needs to be associated with both the exposure and the outcome, but not constitute an intermediate link in the causal chain of events. Confounding can cause an over-, or underestimation of an effect. Provided that the measurement of a potential confounding factor is accurate, confounding can be controlled for in the study design by restriction or matching, or in the data analysis through adjustments in the regression model or by stratification.

In study II, the potential association between declining serum testosterone and impaired sexual function may be subject to confounding by age and treatment. Serum androgen levels decline by age, and so does sexual activity and sexual function [235, 236]. However, declining androgen levels may also be seen as a link in the causal chain between increasing age and decreasing sexual function, and should in this case not be seen as a confounder. The same is true for cancer treatment. The treatment that causes androgen levels to decline can in itself cause sexual dysfunction. Even if an association between, for instance, radiotherapy and decreased androgen levels and low sexual function were established, the impact of other treatment effects are hard to distinguish from the effect of declining androgens levels. In order to adjust for treatment in the correlation tests, FSFI-scores and androgen levels were compared for each treatment group separately.

A large number of factors are thought to influence sexual function in women, such as physical conditions, mental disorders, lifestyle and socio-economic factors, previous experiences, and cultural and religious beliefs [419]. In order to adjust fully for all other potential confounders, we would have needed a much larger material, and therefore we chose the more straightforward method of direct correlation, instead of an adjusted multivariable model, in this pilot setting.

In study IV, confounding from socio-demographic factors and changes in economic benefits over time was reduced by the use of age-, period-, region- and education-matched population comparators. Some residual confounding is possible, since we did not have information on covariates associated with work loss, such as smoking [420], job strain [349], social climate at work [347], and

other economic factors, such as income levels [421]. However, the impact of the latter should be relatively small since sick leave levels before diagnosis/match date were similar among patients and comparators.

External validity

Provided that the results reported in this thesis are not subject to any major biases (threats to the internal validity), the findings could be valid for populations beyond Sweden. The results from study I may not be applicable to populations of other ethnicities since some ethnic variation in AMH has been reported [380]. Also, in study II, the generalizability of our results on sexual function is limited to women in similar circumstances (such as age, partnership status, cancer treatment etc.).

In study III, women's use of HT can be affected by the cost of the medication. The Swedish healthcare system offered prescription drugs free of charge above an annual threshold of SEK 1,800 during the study period. A higher cost may in other countries reduce HT use even further.

Regarding the generalizability of study IV, social systems differ between countries regarding insurance systems for the employed, self-employed and unemployed, the maximum duration of sick leave and the amount of benefit received [343]. In comparison to many other countries, Sweden has generous and comprehensive social security and therefore, our results may not be generalizable to other countries in absolute terms. However, the system was the same for patients and comparators and therefore observed differences between cancer patients and comparators could be generalizable.

PRECISION

Random error is the error that remains when systematic errors have been eliminated. The risk of random errors can be decreased with an increase in sample size. The role of chance can be reflected statistically by p-values or the width of confidence intervals. A hypothesis test of an analysis is based on the null hypothesis, which states that there is no relation between the exposure and outcome, and the result is statistically significant if the observed data deviates sufficiently from the null hypothesis, i.e. $p < 0.05$ and the null hypothesis is rejected. A $p \geq 0.05$ indicates that the null hypothesis cannot be rejected. If the null hypothesis is falsely rejected, a type 1 error has occurred, meaning that a difference is suggested when there truly is none. A type 2 error would occur if the null hypothesis fails to be rejected although it should, meaning that there is a difference but we have failed to identify it.

Sample size is a limitation in studies I and II. Our finding of a reduction in serum AMH and testosterone could be afflicted by type I error, i.e. there actually was no difference. A comparison group would have strengthened the results. In study II, we found no association between testosterone levels and

sexual function, which could be due to lack of power, i.e. a type II error. The reduction in serum testosterone after SOE was similar to the reduction after radiotherapy, but was not statistically significant, which could be due to smaller number of patients in that treatment group.

In register-based cohort studies such as in studies III-IV, the large size of the studied cohorts enhances precision and allows for more stable risk estimation. However, chance can never be excluded as a potential explanation for observed results. In some of our subgroup-analyses, sample size was reduced and the confidence intervals were wide, which makes the specific risk assessment uncertain for these groups.

FINDINGS AND IMPLICATIONS

STUDY I: AMH after cervical cancer treatments

The main finding in study I was that radical hysterectomy and pelvic lymphadenectomy with ovarian preservation was associated with a 45% decline in mean serum levels of AMH one year after treatment, but with no changes in serum levels of FSH and estradiol. The fact that AMH concentrations fell to undetectable levels after chemoradiotherapy and SOE was expected. However, the decline in AMH following radical hysterectomy implies that the surgery affected the women's ovarian function, even though the ovaries were not removed. The women in our cohort had AMH concentrations that could have started to decline more rapidly due to imminent menopause. However, in the general population, mean AMH reduction per year among women of reproductive ages has been reported to be 0.16 $\mu\text{g/L}$ [422] or 5.6% [423], which is less than the 0.9 $\mu\text{g/L}$ decline in AMH found in our study. Still, the sample size of our pilot study was limited, and our suggestive finding could be followed up in larger studies, and ideally include a comparison group.

The decline in serum AMH observed in this study has potential implications for reproduction as well as for menopausal state. The only possibility in clinical practice for a woman to have a biological child after hysterectomy is in vitro fertilization (IVF) and a gestational carrier/surrogate mother. This procedure is not allowed in Sweden, but internationally successful pregnancy outcomes have been described for patients with cervical cancer, also after ovarian transposition and chemoradiotherapy [424, 425]. Recently, uterus transplantation has emerged as a new possibility for women with absolute uterine factor infertility, and has been performed on one hysterectomised woman with previous cervical cancer [426]. The first case of a live birth after uterus transplantation was described in 2015 [427]. AMH levels can in such cases predict future ability to stimulate the ovaries with gonadotropins to acquire eggs for IVF [97].

The other potential importance regarding the decline in serum AMH is that it could indicate a risk of early menopause. Menopause occurs at a median age of about 51 years, dictated by the decline in the number of follicles in the ovaries (the ovarian reserve) with increasing age. Using age and AMH, the age range in which menopause will subsequently occur can be individually calculated. Different models for predicting time to menopause have been developed. In the model by Tehrani et al. [100], age alone had an adequacy of 84% to predict age at menopause correctly, which rose to 92% when AMH was added to the model. An AMH value of 2.0 $\mu\text{g/L}$ in a woman of 30 years predicted a menopausal age of 52 (but with large CI: 42–57), whereas an AMH value of 1.1 $\mu\text{g/L}$ predicted age of menopause to 45 (37–50). In Freeman et al. a decline from 2.0 to 1.1 $\mu\text{g/L}$ would, in the case of a woman 40–44 years of age, imply a reduction of time to menopause of 2.5 years. Women undergoing radical hysterectomy could benefit from assessing their

estimated time to menopause to ensure adequate hormone supplementation in such cases. As these women no longer menstruate, the onset of menopause may go unnoticed.

STUDY II: Testosterone and sexual function after treatment

Study II showed that levels of total and free testosterone decreased slightly after pelvic radiotherapy treatment for cervical cancer among pre- as well as postmenopausal women. Among premenopausal women treated with surgery with SOE, the decline in serum androgen concentrations did not reach statistical significance, maybe due to a smaller number of patients in that group. No direct correlation was found between androgen levels and FSFI scores of sexual function one year after treatment, in line with previous studies on breast cancer patients [158, 163, 164]. However, women with low sexual function at one-year follow-up had higher FSH levels. Serum levels of FSH reflect estradiol levels, and endogenous estradiol levels have been shown to correlate with sexual function in postmenopausal women [428].

Testosterone production declines naturally by age [119] and, theoretically, part of the reduction in serum testosterone observed in this study could be due to the natural effect of ageing. However, the expected age-dependent decline in serum testosterone levels after one year is much smaller than that demonstrated after radiotherapy [429].

The importance of the slight reduction of total and free testosterone after radiotherapy observed in this study is not clear. No single androgen level was predictive of low female sexual function in a large study performed in a healthy non-cancer population [128]. Also in our study, androgen levels were not found to be directly associated with sexual function, but our limited sample size makes the findings uncertain. Our results do not support the hypothesis that serum testosterone values reflect sexual function in cervical cancer survivors, though it cannot be ruled out as a possibility, since we did not have statistical power to adequately examine this association. However, circulating testosterone levels do not necessarily reflect concentrations in target cells. Testosterone may act as a paracrine and intracrine hormone, rather than as a classic hormone [78].

Female sexual dysfunction consists of a continuum of psychosexual disorders and HSDD interrelates with problems of arousal, orgasm, and sexual pain [430]. Many other factors may better predict sexual function in our cohort, such as relationship quality, sequelae of treatment, other chronic illnesses and drugs [430]. A cancer diagnosis can cause increased relationship strain, and studies have shown that cervical cancer survivors are at increased risk of divorce [431, 432].

Many women in our study had higher FSFI scores one year after treatment, contrary to what could be expected. The explanation could be that the women

were affected by their recent cancer diagnosis at baseline, and did not answer the questionnaire as instructed, i.e. according to experiences before start of cancer symptoms. It is also possible that a cancer diagnosis changes priorities and attitudes to life and that cancer survivors can experience a revitalization and positive change of their sexual life and behavior.

Among all women in study II, including the sexually inactive, the lowest FSFI values were found among women who were older and single. Low FSFI scores were also found among women with more advanced tumors. Since coital bleeding is an early symptom of cervical cancer, sexually inactive women are more likely to discover their tumors at more advanced stages.

STUDY III: HT use after radiotherapy or surgical castration

The main finding in study III was that less than half of the women likely in early menopause due to cervical cancer treatment dispensed HT at a recommended dose or close ($\geq 75\%$). Younger women (< 40 years) had a higher prevalence of HT use compared to women aged 40-45 years, but HT use decreased over time in both groups. The higher prevalence of HT use in younger age groups could reflect more severe menopausal symptoms, and thus a more obvious need for treatment. We did not observe any differences in the prevalence or doses of HT among women treated for cervical adenocarcinoma compared with those treated for squamous cell carcinoma, which was unexpected, since HT use after cervical adenocarcinoma has been debated [433].

Our findings of low HT use among women in early menopause have been confirmed in a recent study on HT use among all Swedish women aged 40-44 [434]. Less than 1% dispensed HT, and the occurrence of spontaneous early menopause is expected to be around 5%. A majority of those women dispensed HT less than a year.

Even though the use of HT dispensing as a measure of exposure eliminates bias due to bad recollection and may improve the accuracy of the information on HT use [435], we do not know whether the women used the dispensed medication. Patient adherence to medication in general has been reported to be around 50% [436], but with large variations [437, 438]. Therefore, we cannot exclude that the actual use was lower than that estimated.

We do not know why patients in this study did not use or stopped using HT - if it was because of the patients' own choice or if they were advised to do so by their physician. Treatment guidelines on cervical cancer seldom address the question of HT, which makes the decision to prescribe HT much up to the discretion of the individual gynecologist or oncologist. Our results call for increased awareness among professionals and women of the health benefits of HT up to the age of natural menopause and the lack of evidence for adverse effects of HT in this young patient group.

STUDY IV: Work loss among cervical cancer survivors

Cervical cancer patients had on average more lost workdays than comparators for 8 years following diagnosis, and relapse-free patients had more lost workdays for 4 years versus comparators. We therefore conclude that part – but not all – of the work loss in the cohort was explained by cancer progression or relapse. The long-standing increase in number of lost workdays, and an increased risk of disability pension, was evident among relapse-free patients treated with hysterectomy or chemo/radiotherapy. However, it is also important to point out that the majority of the patients had no registered days on sick leave or disability pension from the second year after treatment and onwards. Also, early-stage patients treated with fertility-sparing surgery had no excess risk, except during the year of diagnosis and treatment.

As in studies of cancer patients in general [343, 344] as well as in gynecological cancer patients [356], our study showed that the majority of the patients did not experience any excess work loss beyond the first year, although the group as a whole had more lost workdays for several years. However, 6% of the patients received disability pension during follow-up, compared to 3% among the comparators. Disability pension in Sweden is a risk factor for increased mortality compared with non-retired persons, even after adjustment for socio-economic factors and underlying disease [439]. Disability pension was 4-6 times higher among patients with previous sick leave (which can be seen as a proxy for co-morbidity not associated with the cancer diagnosis) compared to patients without previous sick leave, and the highest risk was found among patients with previous sick leave and chemo/radiotherapy, thus delineating a high-risk group. Other socio-demographic factors were not associated with disability pension in our study.

We do not know the exact reasons for the increased sick leave and disability pension among relapse-free patients found in this study, but we know from previous studies that cervical cancer survivors experience a plethora of distressful symptoms after treatment. The fact that women with limited treatment had no excess work loss indicates that treatment side effects could explain some of the excess lost workdays.

CONCLUSIONS

- Serum AMH fell to undetectable values after radiotherapy or SOE, as expected. Radical hysterectomy was associated with a decline in AMH one year after surgery, but the sample size was small (n=9) (Study I).
- Testosterone levels in serum declined after radiotherapy. No association was suggested between serum testosterone levels and sexual function scores at one-year follow-up (Study II).
- Less than half of women in early menopause due to SOE or radiotherapy following cervical cancer diagnosis dispensed HT at a recommended dose or close (Study III).
- Women treated with hysterectomy or chemo/radiotherapy – but not women treated with fertility sparing surgery – had an increased risk of sick leave and disability pension several years after treatment, which was only partly explained by cancer progression or relapse (Study IV).

FUTURE RESEARCH

- Fertility preservation for cancer patients depends on determination of risk of fertility impairment by treatment, and an estimate of the length of the remaining reproductive window after treatment. Better prediction models need to be developed for this outcome, where serum AMH is one promising marker that can be used. Also, new techniques for fertility preservation, such as in vitro maturation of immature oocytes retrieved in unstimulated cycles, pharmacological protection of ovaries during chemotherapy, cryopreservation of ovarian cortical tissue and primordial follicle isolation need to be developed further.
- Sexual dysfunction and other distressful symptoms are common after cancer treatment. Minimally-invasive, nerve-sparing surgery as well as sentinel node biopsy for lymph nodal staging may reduce the risk of such complications. More studies are needed to evaluate new surgical techniques.
- Predictors for not using HT following treatment-induced early or premature menopause among cervical cancer patients could be evaluated, in order to improve adherence to medication.
- The morbidity and attitudes behind increased sick leave and disability pension among relapse-free patients need to be identified, in order to develop interventions to improve vocational rehabilitation.

SAMMANFATTNING PÅ SVENSKA

Livmoderhalscancer drabbar kvinnor i alla åldrar och ungefär hälften är under 50 år vid diagnos. Eftersom de flesta blir botade, kommer många kvinnor att leva länge med konsekvenserna av sjukdomen och dess behandling.

Livmoderhalscancer kan behandlas genom att operera bort livmodern, och ibland också äggstockarna, samt med strålbehandling och cellgifter. Om tumören är liten kan det ibland räcka med att bara ta bort en bit av livmoderhalsen, s.k. cervixamputation eller trachelektomi, och då kan kvinnan fortfarande bli gravid och få barn. Yngre kvinnor som genomgår strålbehandling, eller där äggstockarna opereras bort, hamnar omedelbart i klimakteriet. Om kvinnan är under 50 år vid cancerbehandlingen rekommenderas sedan östrogenbehandling upp till minst 50 års ålder mot klimakteriebesvär och för att minska risken för hjärt-kärlsjukdom och benskörhet. Efter behandling mot livmoderhalscancer är det vanligt att kvinnorna får symtom från tarm och urinblåsa, bensvullnad och sexuella problem.

Syften med avhandlingen var att undersöka hur hormonnivåer i blodet påverkas av cancerbehandling, om yngre kvinnor som hamnar i klimakteriet p.g.a. behandlingen använder östrogen, samt och i hur hög utsträckning kvinnor som haft livmoderhalscancer är sjukskrivna jämfört med befolkningen.

Studie I: Anti-Müllerskt hormon (AMH) utsöndras från äggstockarna och kan mätas i blod. Nivån av AMH tros kunna förutsäga ungefär om hur lång tid kvinnan kommer att hamna i klimakteriet. Vi mätte AMH i blodet hos 29 kvinnor under 45 år före och efter olika behandlingar för livmoderhalscancer. Vi fann att nivåerna blev omätbara om kvinnan fått strålbehandling eller opererat bort äggstockarna. Om livmodern opererats bort men äggstockarna lämnats kvar, minskade AMH med nästan hälften, vilket skulle kunna innebära en risk att kvinnan hamnar i klimakteriet tidigare än hon annars skulle ha gjort.

Studie II: Testosteron tror man har betydelse för allmänt välbefinnande och sexualitet hos kvinnor, men man vet inte hur testosteronnivåer i blodet påverkas av behandling för livmoderhalscancer. Man vet inte heller om sexuella besvär efter behandling kan bero på låga testosteronnivåer. Vi mätte testosteron i blod hos 60 kvinnor i alla åldrar före och efter olika behandlingar för livmoderhalscancer, och kvinnorna fick samtidigt fylla i formulär angående sexuella besvär. Vi fann att testosteron minskade efter strålbehandling. Däremot kunde vi inte hitta några samband mellan testosteronnivåer och sexualitet.

Studie III. Vi sammanställde information från Cancerregistret, Patientregistret och Läkemedelsregistret på uthämtade recept på läkemedel med östrogen bland kvinnor under 45 år som haft livmoderhalscancer och som behandlats

med strålning eller borttagande av äggstockarna. Vi fann att mindre än hälften av kvinnorna använde östrogen i rekommenderad dos, eller minst tre fjärdedelar av full dos, under det första halvåret efter behandlingen. Många slutade också använda östrogen under de närmast följande åren. Det kan innebära en risk att dessa kvinnor senare drabbas av hjärt-kärlsjukdom och benskörhet. Både kvinnor och läkare kan behöva informeras om att östrogenanvändning före 50 års ålder rekommenderas och bedöms vara fördelaktig för dessa kvinnor.

Studie IV: Vi sammanställde information från Cancerregistret, Patientregistret och Försäkringskassan om sjukskrivning och förtidspension bland kvinnor som haft livmoderhalscancer, och jämförde med en kontrollgrupp kvinnor som inte haft livmoderhalscancer men som hade motsvarande ålder, utbildning, uppföljningstid och bodde i samma sjukvårdsregion. Vi fann att kvinnor som haft livmoderhalscancer, och inte hade några tecken på återfall i registren, hade mer sjukskrivning och förtidspension under de 4 första åren efter sin sjukdom. Risken för förtidspension var större hos alla kvinnor som behandlats för livmoderhalscancer, förutom för dem, som endast genomgått mindre kirurgi (d.v.s. enbart operation av livmodertappen). Den ökade sjukfrånvaron bland kvinnor som haft livmoderhalscancer kan bero på biverkningar av behandlingen, även om andra orsaker kan gälla för enskilda kvinnor i studien.

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APPENDIX

Codes used for classification of cervical cancer treatment.

Cervical cancer treatment	NOMESCO/KKÅ/KVÅ/CD10 codes
Study III	
Cervical resection	LDC00, LDC03, LDC10, LDC96
Hysterectomy	LCD00, LCD01, LCD 04, LCD 10, LCD 11, LCD 30, LCD 31, LCD 40, LCD 96, LCD 97
Unilateral oophorectomy/SOE	LAF00, LAF01, LAE10, LAE11
Bilateral oophorectomy/SOE	LAF10, LAF11, LAF20, LAE20, LAE21
Pelvic lymphadenectomy	PJD55, PJD45
Radiotherapy	Z510, Z08.1, Z92.3, Z08.7, DV013-DV018
Chemotherapy	DT107, DT108, DT116, Z511, Z512
Trachelectomy	LDC00, LDC03, LDC10, LDC96 in combination with PJD55, PJD45
Study IV	
Hysterectomy	LCD00, LCD10, LCD30, LCD11, LCD01, LCD31, LCD96, LCD04, LCD40, LEF13
Cervical resection/conisation	LDC10, LDC03, LDC96, LDC00, LDB00, LDW96
Pelvic exenteration	LCE00, LCE10, LCE20, LCE96
Radiotherapy/ Follow-up examination	ZV031, ZV033, DV012-DV018, DV070, DV071, Z510/Z081, Z923
Chemotherapy/ Follow-up examination	DT107, DT108, DT116, Z511/Z082
Follow-up examination after combined treatment	Z087
Secondary malignant tumor	C77, C78, C79

SOE=salpingo-oophorectomy